Université de Sherbrooke

Influence of age and comorbidities on the level of high sensitive cardiac troponin T (hs-cTnT) in the geriatric population

By:

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RÉSUMÉ - Objectif de l'étude : Nous avons déterminé la valeur prédictive de la troponine T cardiaque de haute sensibilité (TnTc-hs) chez les patients âgés et très âgés afin de diagnostiquer plus précisément les événements coronariens aigus, en particulier chez les patients atteints de maladies concomitantes.

Matériels et méthodes:

Nous avons évalué rétrospectivement 6 977 dossiers médicaux de patients âgés de ≥ 65 ans admis au CHUS CIUSSS-Estrie ayant eu une mesure en série TnTc-hs. Le premier échantillon sanguin pour la mesure de TnTc-hs qui a été recueilli au moment de l'admission a été pris en compte. Les patients âgés ont été regroupés en trois groupes d'âge : les patients âgés de 65 à 74 ans (jeunes âgés), les patients âgés de 75 à 84 ans (âgés) et les patients âgés de 85 ans et plus (très âgés). Ensuite, ils ont été divisés en 3 catégories selon le tertile TnTc-hs concentration avec tertile 1 (0-14 ng / L = niveau bas), tertile 2 (15-31 ng / L = niveau modéré) et tertile 3 (≥32 ng / L = niveau élevé). Dix-sept comorbidités ont été identifiées ultérieurement dans notre échantillon. Les patients ont été regroupés en quatre catégories selon la présence de comorbidités avec : quartile 1 (une ou deux comorbidités), quartile 2 (trois comorbidités), quartile 3 (quatre à cinq comorbidités) et quartile 4 (≥ 6 comorbidités).

Résultats :

Trois mille quatre cent trente-neuf patients de sexe masculin (50,4%) ont été inclus dans l'étude. Deux mille quatre cent quatorze patients ont eu six comorbidités ou plus (35,4%). Pour notre cohorte, dont l'âge moyen était de 78,3 ans, le taux TnTc-hs était de 79,9 ng / L. Chez les deux sexes, la valeur de la troponine dans tous les groupes d'âge, avec tous les types de comorbidités, était remarquablement élevée. En outre, l'odd ratio (OR) de la dose élevée et de la dose modérée de troponine a été trouvéle plus faible chez les groupes jeunes âgés et âgés ($p < 0,001$). L'augmentation de l'âge et le nombre de comorbidité pourraient augmenter les chances d'avoir des taux élevés de TnTc-hs ($p <0,001$),mais étonnamment, en ce qui concerne l'OR ajusté, si l'on considère une année de vieillissement et une comorbidité en continu, les troponines surélevées sont influencés plus significativement par la comorbidité, comparativement au vieillissement ($p <0,001$)

Conclusion :

En ce qui concerne l'étude actuelle, une élévation globale des valeurs de TnTc-hs dans tous les groupes de comorbidités a été détectée. De plus, bien que l'âge avancé puisse être associé à une élévation de TnTc-hs (OR =1,07, $p<0,001$); en revanche, l'élévation de la troponine

cardiaque résulterait plus de comorbidités préexistantes (OR=1,31 pour le groupe jeune âgé et OR=1,22 pour le groupe âgé, p <0,001). Par conséquent, une valeur élevée de TnTc-hs devrait être considérée comme étant d'origine pathologique et l'éthologie spécifique devrait être recherchée

Mots-clés: TnTc-hs, patients âgés et très âgés, comorbidités.

Abstract. – A high level of troponin correlates significantly with the risk of death or recurrence of myocardial infarction. However, most of these studies have been obtained in middle-aged people. It is considered that ageing is associated with increased troponin levels. This can be a major drawback for the stratification and diagnostic of acute coronary syndrome in elderly patients. Our study was designed to determine the predictive value of high-sensitivity cardiac troponin T (Hs-cTnT) in the elderly and very elderly patients and mainly in the presence of concomitant diseases.

Materials and Methods: We retrospectively evaluated 6 977 medical records of patients aged ≥ 65 years and admitted for patients admitted to the hospital for chest pain. Three age groups were formed: patients aged 65 to 74 years (young-old), patients aged 75 to 84 years (old) and patients ≥85 years old (old-old). Three categories were formed according to the Hs-cTnT levels: 0-14 ng/L, 15-31 ng/L and ≥32 ng/L. Seventeen comorbidities were identified and patients were grouped into four categories according to the number of comorbidities: 1 or 2 comorbidities, 3 comorbidities, 4-5 comorbidities and ≥ 6 comorbidities.

Results:3 439 male patients (50. 4%) were included in this current study among which 2 414 patients had six or more comorbidities (35.4%). For our cohort, whose average age was 78.3 years, the Hs-cTnT level was 79.9 ng/l. In both sexes, the troponin value across all age groups, with any types of comorbid disease excluding any cardiac diseases, was remarkably high compared to the normal troponin values ($p<0.05$). Our results also demonstrated that the Hs-cTnT levels increased in the presence of comorbidities independently of their number ($p<0.05$). In the old-old group the troponin levels decreased even when comorbidities were present suggesting that age is not the determinant factor in the troponin increase.

Conclusion: Advanced age could not be associated to an elevation of Hs-cTnT; in contrast, cardiac troponin elevation was the result of pre-existed comorbidities independently of their number. Increased troponin level in elderly should always be considered as pathological and a specific etiology searched.

Key words: Hs-cTnT, elderly and very elderly patients, comorbidity

Je dédie mon mémoire à:

Mes parents. C'est leur amour qui m'aura porté si loin.

Ma chère épouse, Elmira, et à mon adorable fille, Hasti:

Aucune dédicace ne saurait exprimer tout l'amour que j'ai pour vous, Votre joie et votre gaieté me comblent de bonheur.

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TABLE DES MATIÈRES

LIST OF TABLES

LIST OF FIGURES

LISTE DES ABRÉVIATIONS

FMSS	Faculté de Médecine et des Sciences de la Santé
HS-cTnT	High-Sensitivity Cardiac Troponin T
HS-cTnI	High-Sensitivity Cardiac Troponin I
AMI	Acute Myocardial Infarction
ACS	Acute Coronary Syndrome
UA	Unstable Angina
ACC/AHA	American College of Cardiology/American Heart Association
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
ECG	Electrocardiogram
NSTEMI	Non-ST Elevation Myocardial Infarction
cTn	cardiac Troponin
cTnT	cardiac Troponin T
cTn I	Cardiac troponin I
CHUS	Centre Hospitalier Universitaire de Sherbrooke
COPD	Chronic Obstructive Pulmonary Disease
RI	Renal Insufficiency
AHTN	Arterial Hypertension
NCD	Neurocognitive Disorders
PHTN	Pulmonary Hypertension
PE	Pulmonary Embolism
CVA	Cerebrovascular Accident
ASVD	Atherosclerotic Vascular Disease
SAH	Subarachnoid Hemorrhage
CVD	Cardiovascular Disease
CHF	Congestive Heart Failure
CIUSSS	Centre intégré universitaire de santé et de services sociaux
NVSS	National Vital Statistics System
PHAC	Public Health Agency of Canada
NHLBI	National Heart, Lung, and Blood Institute
ARIC	Atherosclerosis Risk In Communities
CIHI	Canadian Institute for Health Information

FDA	Food and Drug Administration

INTRODUCTION

Over the next thirteen years, the world's population is estimated to rise from 7.6 billion (in mid-2017) by more than one billion people, reaching 8.6 billion in 2030, rising to 9.8 billion in 2050, and 11.2 billion in 2100(UN, 2015). The number of people 60 years old and over is estimated to be 962 million, 13% of the total population in mid-2017. The annual growth rate for this age group has been estimated approximately three percent(UN, 2015).According to the United Nations report, the world's population is dramatically continuing to become old. Almost, all countries have shown an increase in number and percentage of elderly in their population. In other words, the number of people aged 60 years and older has increased significantly in most countries and regions in recent years and is expected to increase rapidly in the coming decades.

The fastest growth rate of the elderly between 2000 and 2015 has been demonstrated in high-income countries and is expected to show the same between 2015 and 2030(UN, 2015). It is expected that the growth in number of elderly will increase rapidly between 2015 & 2030, in upper-middle-income countries too.

Considering this projection, between 2017 and 2030, the number of aged people 60 years and over will increase by 56 per cent, from 962 million to 1.4 billion, and by 2050, the world population of elderly is projected to more than double its size in 2017 (Fig. 1), reaching nearly 2.1 billion, and will reach to 3.1 billion in 2100.

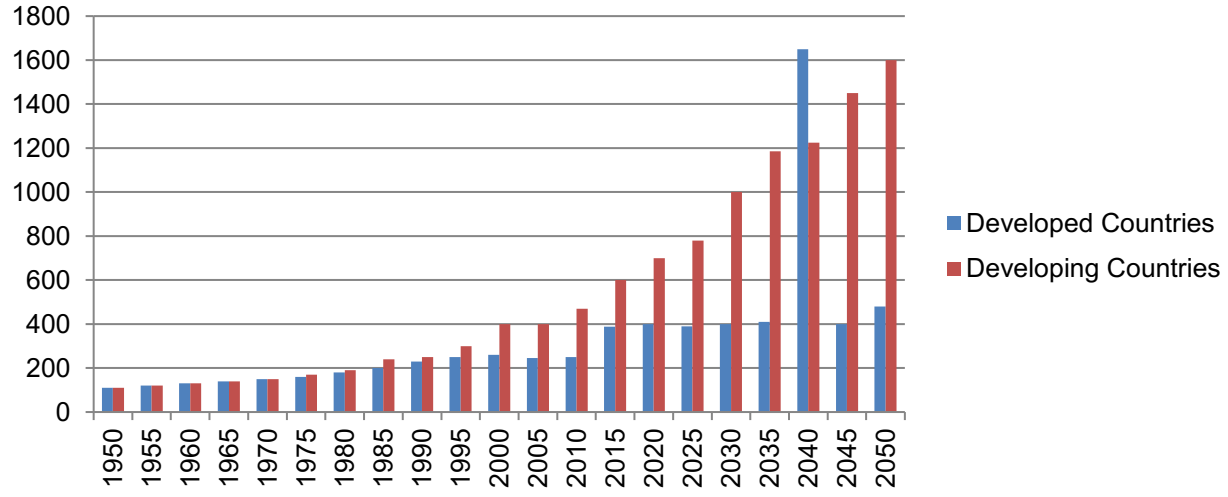

Figure 1. Number of people aged 60 or over; World, developed, and developing country, 1950 – 2050.Source: UNDESA, World Population Ageing 2011 (2012; forthcoming), based on UNDESA Population Division medium projection scenario, World Population Prospects: The 2010 Revision.

This report also projects that, the growth rate of population aged 80 or over, who is called the ″oldest-old″ persons, will increase faster than the rate of older population (Figure 2)

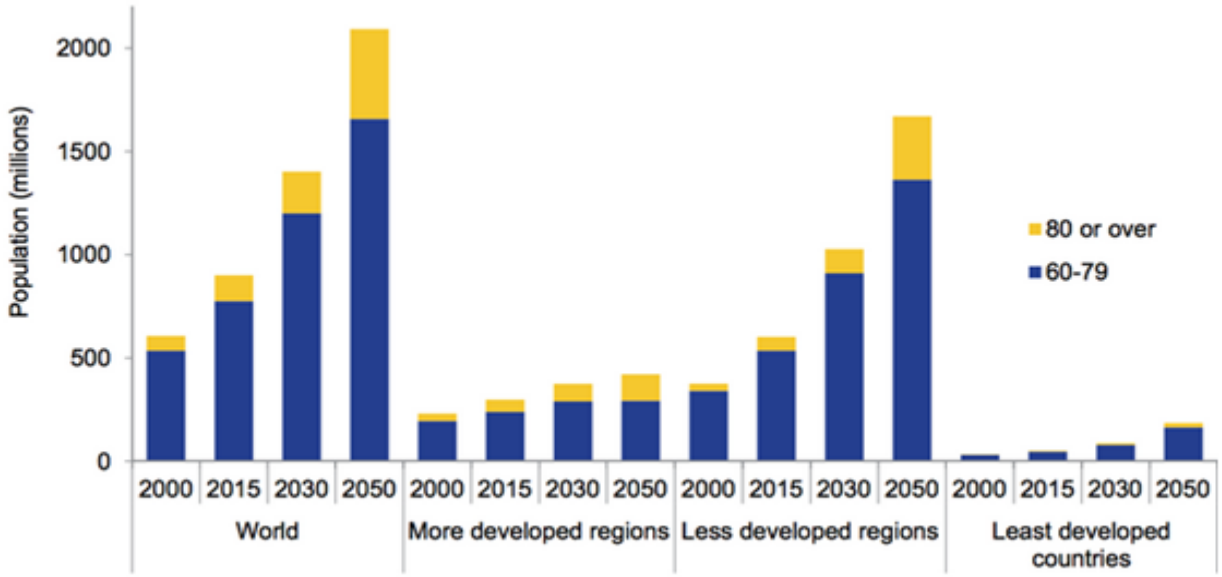

Figure 2. Population aged 60-79 years and aged 80 years or over by development group, 2000, 2015, 2030 and 2050, Data source: United Nations (2015). World Population Prospects: The 2015 Revision

In this way, the oldest-old population, from 137 million in 2017 will reach to 425 million in 2050, and it is estimated that in 2050 having more than tripled in numbers compared to 2017 (Fig.3).

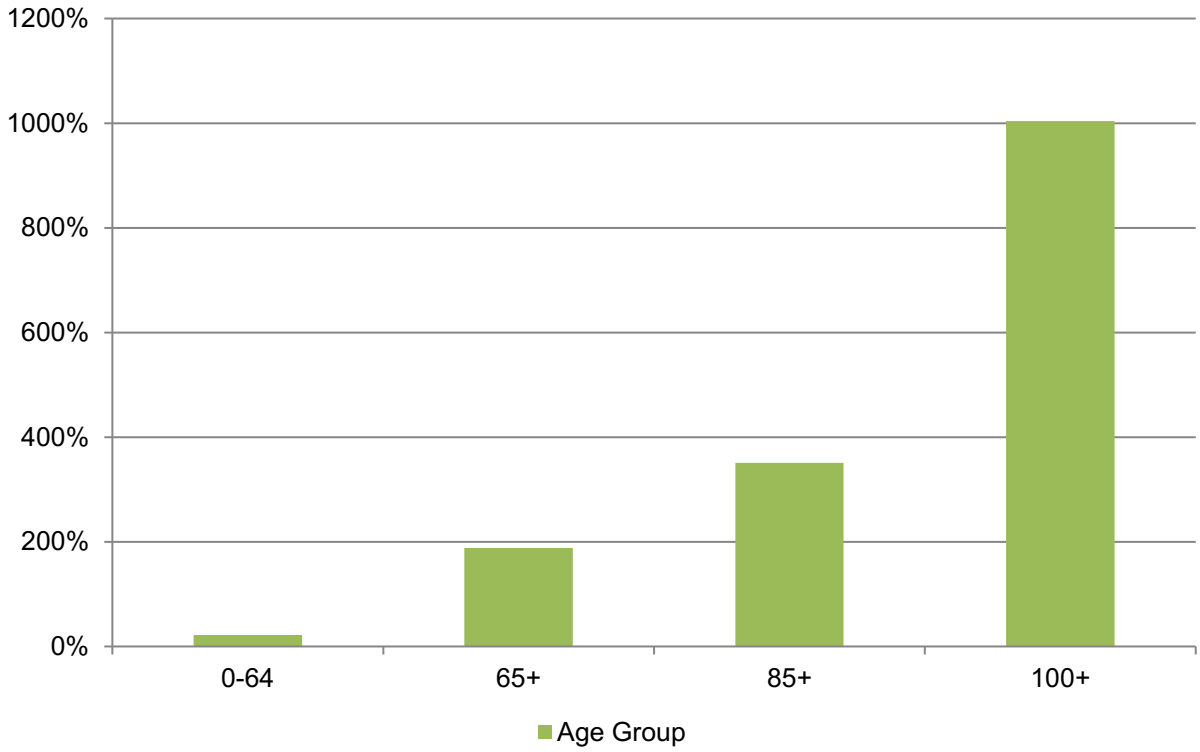

Figure3. The expected percentage change in the world's elderly population, by category, from 2010 to 2050.Reconstructed from:United Nation, world population prospect,Available at:https://www.un.org/development/desa/en/news/population/world-population-prospects-2017.html

The number of people reaching 80 or over will exceed 909 million in 2100, showing the increase by almost seven times its value in 2017.

In the United States of America (USA), the percentage of people aged 60 and over in 2015 has been calculated as 24.6%, and for years 2050 and 2100, it has been projected as 36.2% and 44.1% of the population respectively(UN,2015).

For Canada, the proportion of the population aged 65 and over grew from 14.1% in 2006 to 16.6 % in 2016(Statistic Canada,2017). For the first time, the number of Canadian seniors aged 65 and older surpassed the persons under 15 years of age in 2015 (Statistic Canada, 2015). The projected growth scenario is expected to be further increasing the future population of the elderly

in Canada. According to the United Nations, the percentage of aged people for years 2050 and 2100 in Canada will reach to 43% and 50.4% respectively(UN, 2015).

According to three demographic projections named low-growth, medium growth & high growth scenarios, referring to population growth rate that has been presented by Statistic Canada (Fig.4), both overall numbers & proportions of people aged 80 years and over are rising rapidly in Canada in the near future.

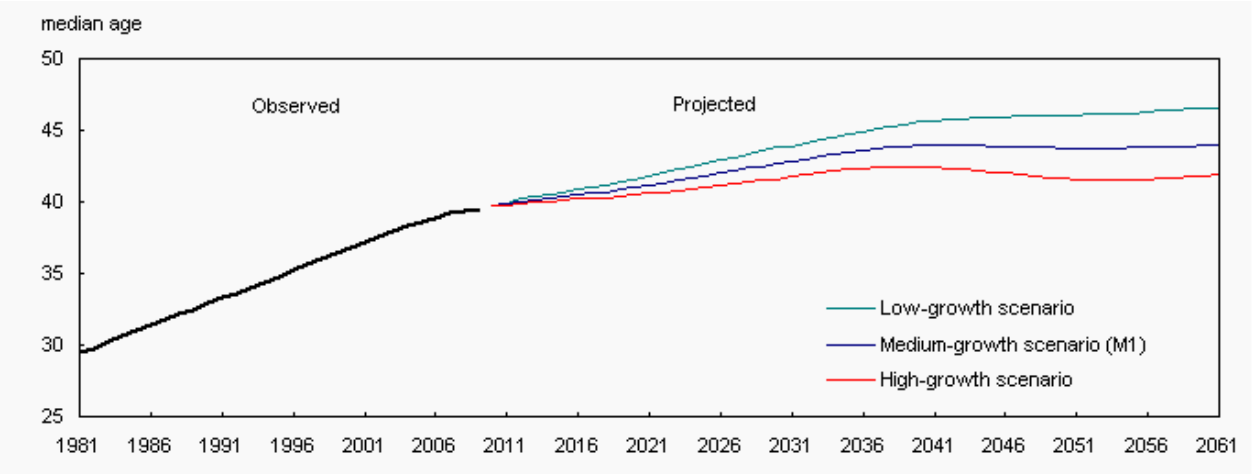

Figure 4.Median age observed (1981 to 2009) and projected (2010 to 2061) according to three scenarios, Canada. Available at:http://www.statcan.gc.ca/pub/91-520-x/2010001/ct010-eng.htm.

The main issues that emerge

Obviously, dramatic growth in numbers and proportions of the senior population, not only puts a heavy pressure on health systems and requires further demand for medical services, but also increases the risk of diseases associated with age.

The main reasons assigned for accompanying of the growth of the ageing population and increase of life expectancy can be concluded as: (1) Prevention, treatment and control of the transmission of communicable diseases as a result of advances in medicine, adoption of modern technology in public health and public health services development. (2) Implementation of successful strategies for pandemic control. (3) Possible elimination of large-scale wars. (4) Improvement of standards of living and (5) Revolution in favor of agricultural systems (food production and food security), (Giannitsis,et al., 2010).

It is acknowledged that the elderly patients are poorly represented in clinical studies. It is estimated that the older individuals were excluded up to 35% in the published studies(Shenoy et

Harugeri,2015,Lee, ,Alexander, Hammill, Pasquali, Peterson,2001 ,Masoudi, et al., 2003), which contributes to lack of knowledge and understanding of the process that may contribute in developing age-related diseases that undermines the diagnostic criteria for this group. The cost of ignoring old people, particularly very old people from research trials, not only threatens their well-being by lacking of knowledge and understanding of the process that may contribute in developing age-related diseases that undermines the diagnostic criteria for this age group, but it can significantly influence physician's decision making process.

Physiopathology of ageing

Although there are no tools to define ageing precisely from the medical perspective, it has been defined as a sum of all changes that occur in living organisms, which appears over time, and inevitably lead to senescence (Levine, 2012).Actually, aging is defined as a subtle, progressive and irreversible process which appears slowly during years with different rate among people (Roger, 2007) that result from a continuous biological accumulation of many different types of damages caused by molecular defects that augment in cells and tissues.

Although many theories exist that explain the aging, there is no a single theory that defines the ageing process reasonably & comprehensibly (Hayflick, and Moorhead, 1961)Amongst different possible theories that explain the mechanism of ageing, Dr. Hayflick et al., suggested a phenomenon, which refers to a restriction for cellular division in human, known as ″The Hayflick Limit Theory″(Hartman,1956). According to this theory, this limitation may result from several different factors including genetic misconstruction as telomere shortening, activation of different oncogenes as well as aberrations in genetic pathways, release of free radicals during oxidative stress conditions that raise with aging that leads to intracellular damages, abnormally elevated inflammatory markers and increase in apoptosis(programmed cell death). In 1956, Dr. Denham Harman(Erbas and Sekerci, 2011)proposed the free radial theory of ageing, considering ageing as a consequence of imbalance between the productions of Reactive Oxygen species (ROS) or oxygen free radicals and antioxidant protection systems. A free radical is defined as any highly reactive atom or molecule that contains at least a single unpaired electron in an outer shell mainly produced as mitochondrial respiration (Cheeseman and Slater, 1993; Wennberg, 1999). Based on this theory, advanced accumulation of oxidative DNAcauses cellular damage that is a synergistic factor leading to aging.

However, ageing-induced changes could be observed in essentially tissues, organs and organ systems. These changes not only lead to a variety of consequences in tissue and organ dysfunction but also influence clinical presentation of diseases.

Considering the genetic and environmental influence on human aging, there are no specific ages at which people become exactly aged or very aged. By tracking a sample of subjects from birth,it can be proven that the risk of developing a disease would vary as the birth cohort aged, thus, confirming the role of aging as an important and non-modifiable contributor in many diseases. It can be derived that it is inevitable to define ageing according to chronological models. Therefore, it has been accepted as a convention, an individual aged 65 year or more be called as the elderly(Batchelor et al., 2000; WHO, 2012).

Age related changes could be aggravated by specific comorbidities or pre-existingconditions. Consequently, the presence of comorbidities with ageing may affect functioning, quality of life and mortality. These conditions potentially can increase the risk when comparing with the condition that might be expected in the younger adults(CIHI, 2011).In other words, comorbidities that mostly accompany in aged people can mainly lead to a worse prognosis and consequently increase of both mortality and morbidity of acute heart conditions in elderly. Therefore, ageing and comorbidities are two conditions that have strong relation in medical practice.

Almost three quarters of Canadians and Americans seniors over 65 have at least one to three chronic conditions respectively (Alami,Fanf,Song,Nacamuli,2003; LeRoyet al.,2014).

A number of different processes are more associated with ageing, and have direct impact on cardiovascular health, function, and clinical decision making relative to heart conditions. Ageing process involves progressive and often functional impairments in across multiple organ systems. As a result, this can significantly lead to major morbidity and mortality and affect the pharmacokinetics and pharmacodynamics of medication in the elderly(Kajstura, 1996; Schwartz, 2007).

The main changes in the heart structure with ageing result in loss of cardiomyocytes, due to necrosis or apoptosis (Lie et al.,1988), which stimulates the hypertrophy of the remaining cardiomyocytes, increase of the connective tissue accumulation (fibrosis), and amyloid deposition in very old individuals (Gerstenblith,1977). Loss of cardiomyocytes can cause excessive cells stretching and atrial wall stiffening impose an increased vascular load, leading to left ventricle walls thickness(Lakatta, 2007).

In the elderly, due to an increased amounts and concentration of collagen and decrease levels of elastin in the arterial wall, arterial compliance is normally decreased (Yu and Chung, 2001; Maruyama, 2007).In the above population, the blood vessels, the endothelial function is also abnormal because the production of nitric oxide (NO) is reduced by decreasing NO-dependent dilation. In addition, other bimolecular changes such as increases in specific matrix metalloproteinase, transforming growth factor-beta 1, and angiotensin II, contribute to endothelial dysfunction (Martz et al., 2000). Moreover, NO bioavailability decreases with aging(Van der loo et al., 2000).Subsequently, it has mostly been assumed that the reduction of bioavailable nitric oxide is secondary to increased oxidative stress during ageing (Pugh,et al., 2001; Webb, et al., 2005). The structural and functional changes in the heart with aging have shown in figure 5.

Stiffening of the great arteries may promote an increase in systolic blood pressure, a decrease in diastolic pressure and widening pulse pressure(Yu, B. P., and Chung, 2001). Meanwhile, the effect of aging on the other systems may affect cardiovascular system that could be exemplified by aged-induce decrease in the testosterone production of the endocrine system resulting in changes to distribution of the cardiac contractile proteins (Tsang,et al., 2002).

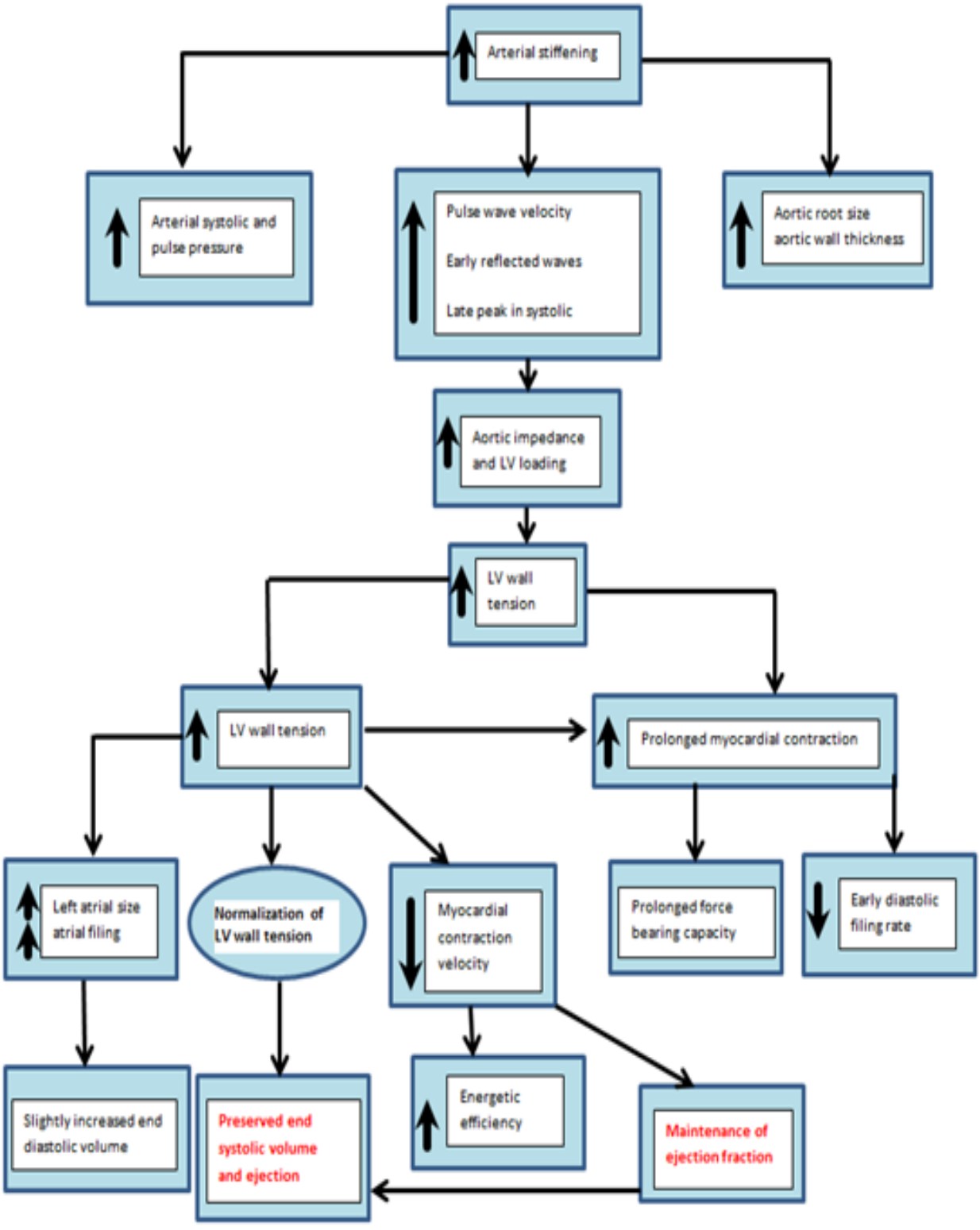

Figure 5.Ageing induced changes in cardiovascular system in healthy subjects.Modified from Lakatta, EG: Cardiovascular regulatory mechanisms in advanced age. Physiol. Rev 73: 413–465, 1993

The main age-associated changes in the cardiovascular system that contribute in morbidity and mortality could be summarizedas follows:

- The cardiac mass in elderly usually is increased(Pearson, ,et al.,1997)
- Endothelial dysfunction which enhances vasoconstriction
- Heart rhythm disorders (Hees, et al.,2004)
- Increased systolic blood pressure, even if they are normotensive (Beck,2000)
- Left ventricular hypertrophy as excess thickening of the left ventricle
- Arterial stiffness as an increase in both systolic blood pressure & pulse pressure
- Diastolic ventricular dysfunction (early diastolic filling of the ventricles is reduced), that could deteriorate diastolic filling abnormalities (Yazdanyar et al.,2009)
- Decreased cardiac reserve (the heart cannot achieve its maximum capacity when needed)
- The heart pumping would be in an arrhythmic fashion because the cardiac action potentials are prolonged
- Cardiac-induced renal dysfunction(WHO,2010)(inability to maintain composition and volume of body fluid)

The effect of ageing on the heart could be exemplified by referring to increased occurrence of acute coronary syndrome (ACS) or acute myocardial infarction (AMI) inthe elderly. In spite of the fact that aging alone should not necessarily be considered linked to ACS or AMI, the majority of epidemiological studies concerning AMI or ACS have been significantly demonstrated that ageing is associated with a sharp rise of these cardiac diseases(Orimo, et al., Pal Yu, et al.,Yu,2006;Roger,2007).

The correlation between the physiological processes of aging and age-related pathological processes has been demonstrated (Extermann, et al., 2005, Carroll and Miller, 2010).Consequently, aging may alter the clinical manifestation, response to treatment, and outcomes of diseases. Therefore, the observations regarding the performance of a clinical trial in accordance with the young population may not apply in elderly patients.

It is important to identify with precision the major causes of death in the elderly and the extreme elderly as well, in order to change mortality rates among the older population.Given the differences in physiological reserves, comorbidities, functional capacity, and geriatric

syndromes, the elderly reveal a heterogeneous population(HALE project, 2004).These criteria may influence the clinical symptoms, even may modify the clinical consequences. As a result, it seems inappropriate to assume that the elderly benefits of the same clinical approach as for the younger population. Furthermore, elderly patients may not represent the same predetermined outcomes in paraclinical investigations.

In conclusion, risk of developing morbidity and mortality of ACS or AMI has been significantly increased with aging (WHO,2015). The impact of ACS or AMI among older adults has been integrated by reducing homeostatic reserves, increasing prevalence of comorbidity, increasing polypharmacy and creating more complex social issues.

Cause-specific mortality in elderly

The global outbreak of non-communicable diseases is mainly related to aging. Although there is a worldwide difference to present the secondary causes of death in the elderly among stroke, cancers or respiratory diseases, there is a global consensus regarding the role of Ischemic heart diseases (IHD) as a main cause leading to death among older people (HALE project, 2004,WHO,2015).

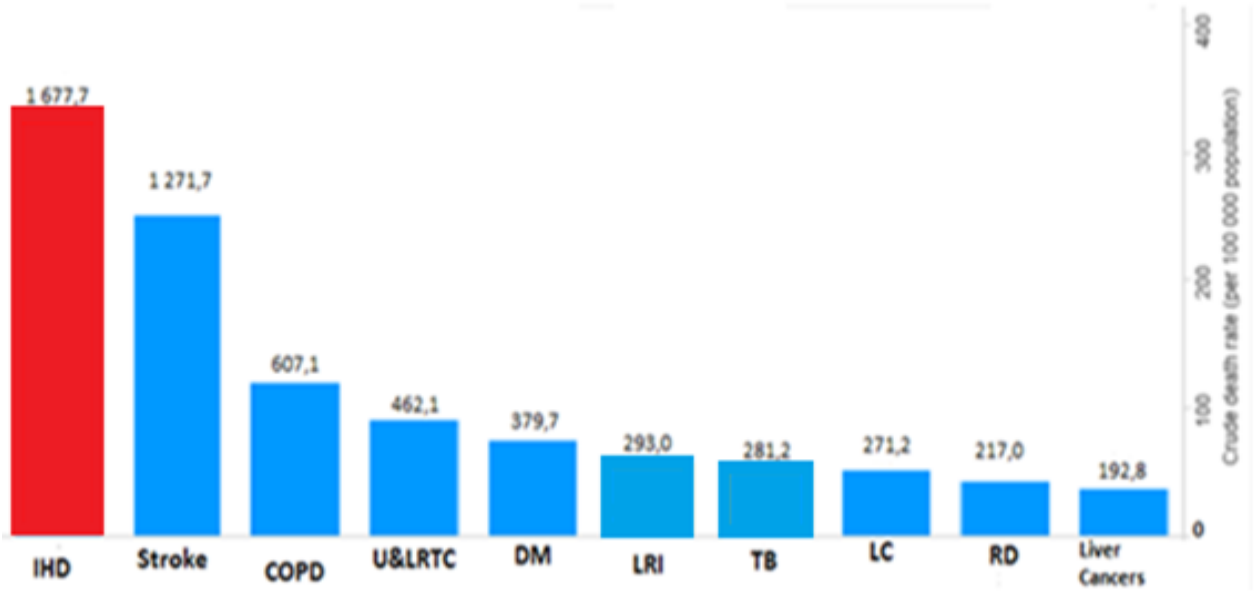

Figure6. The 10 main global mortality causes in people aged 60-69 years, in 2015, IHD=Ischemic Heart Disease, COPD=Chronic Obstructive Pulmonary Disease,L&URTC=Lower and Upper Respiratory Tract Cancers,DM=DiabetesMellitus, LRI=Lower Respiratory Infection, TB=tuberculosis, LC=Lung cancers, RD=Renal Diseases,Modified from:http://www.who.int/gho/mortality_burden_disease/en/

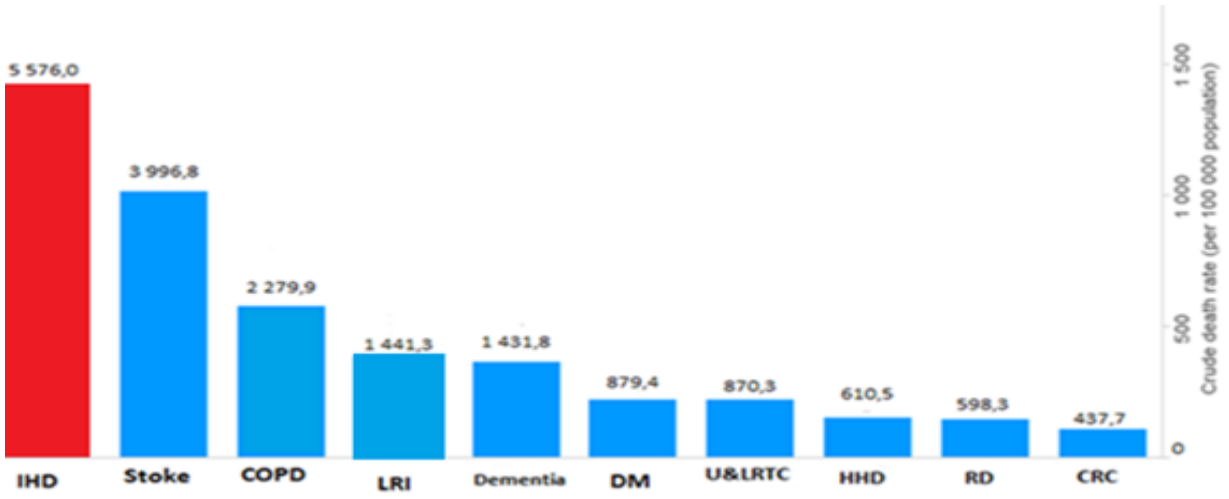

Figure 7. The 10 main global mortality causes in people aged 70 years and over, in 2015,IHD=Ischemic Heart Disease, COPD=Chronic Obstructive Pulmonary Disease, LRI=Lower r respiratory Infection, DM=Diabetes Mellitus L&URTC= Lower and Upper Respiratory Tract Cancers, HHD=Hypertensive Heart Disease, RD=Renal Diseases, CRC=Colorectal CancerModified from http://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/

CHD is the most common cause of death worldwide, in both men and women(Scarborough, Wickramasinghe, Bhatnagar, and Rayner, 2011; Lloyd-Jones, Gersh. 2008; Mozaffarian, et al., 2015). Despite recent progress in the prevention and treatment of cardiovascular disease with adopting a healthy lifestyle such as regular exercise and physical activity, developing healthy eating habits or a balanced diet to have a healthy weight, that could help to reduce the rate of CHD in elderly (WHO,2008;Statistics Canada,2015;Ibanez, et al,2017). However, cardiovascular diseases are reported as the main cause of death in the elderly in all economic levels (low, middle, & high income) of many countries (Statistics Canada,2012).

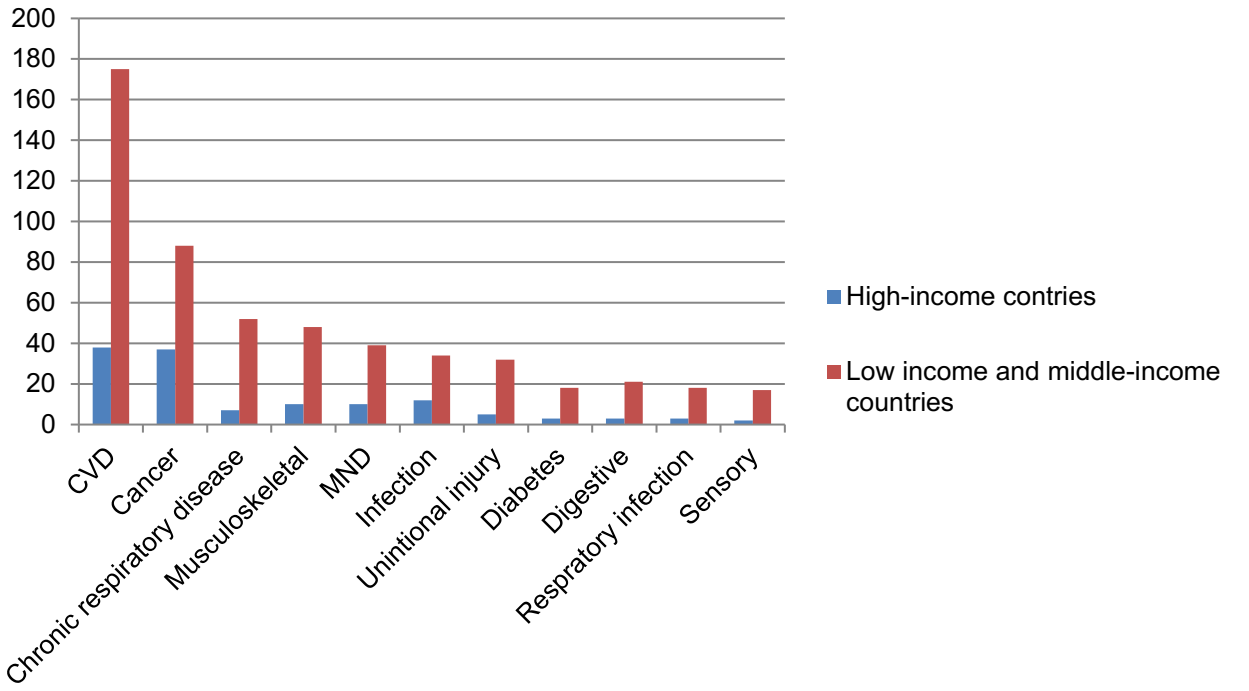

Figure 8.Leading contributors to burden of disease in people aged 60 years and older in 2010—DALYs (million) by cause and World Bank income.DALYs=disability-adjusted life years. CVD=cardiovascular and circulatory diseases. MND=mental and neurological disorders, combining the IHME GBD mental and behavioral disorders and neurological disorders groups.

The main causes of death in elderly in Canada

Given that the Canadian population is aging, it can be expected that in the near future an increasing number of people with heart disease will be observed. In Canada, the highest incidence of heart disease has been reported with the groups aged 65-79 and 80 and older, 15% and 24% respectively (Alexander, et al., 2005; WHO, 2017). The age adjusted incidence of acute myocardial infarction is 10 times higher in aged group 65-74 compared to aged group 35-44, amounting to 70,000 acute myocardial events yearly. According to statistics Canada, heart diseases are the second leading cause of death for people aged 65 years and over (Fig.9).

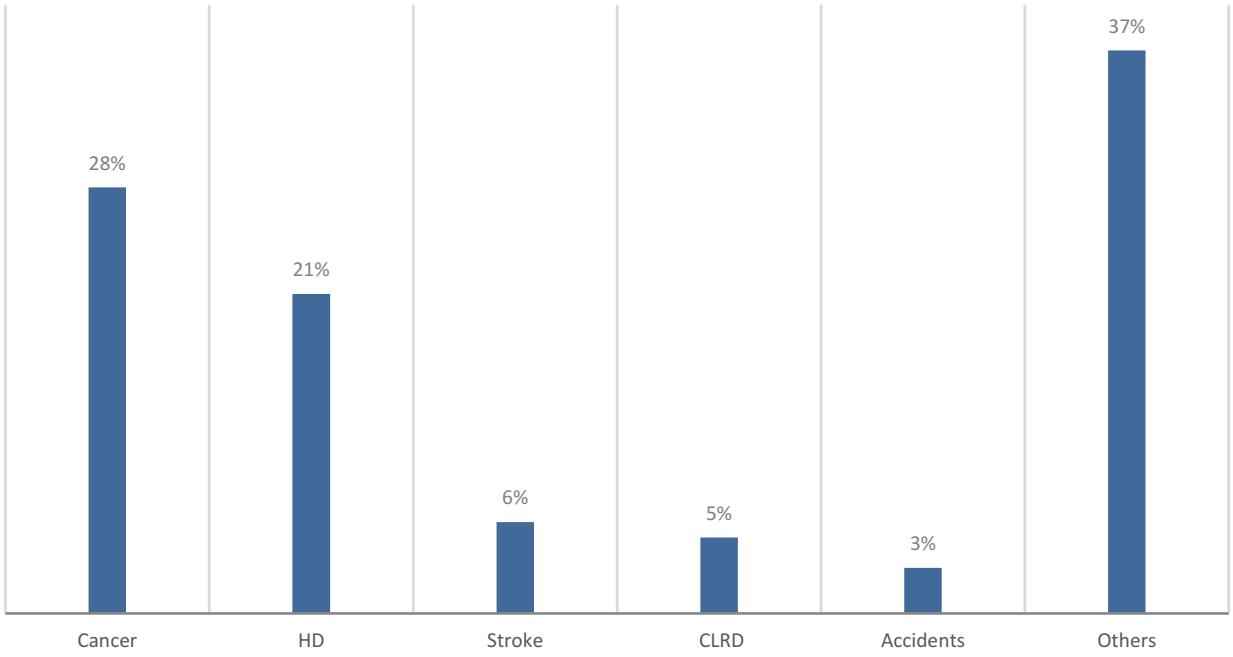

Figure 9.Death Database, CANSIM Table 102–0561., HD= Heart Diseases, CLRD=Chronic Lower Respiratory Disease, Modified from: Vital Statistics. Modified from:http://www.statcan.gc.ca/pub/82-625-x/2017001/article/14776-eng.htm

Epidemiology of acute coronary syndrome

About 33% of all ACS events happen in patients aged over 75, and they give reason for almost 60% of all-cause mortality (Savonitto, Morici, and De Servi, 2014).The worldwide fatality rate of ACS in 2015 has been estimated 7.6 million deaths per year (Braunwald, and Bonow, 2014).Elderly patients, who are suffering from ACS, make a prominent part of hospitalized patients; this will be significantly increased in the near future(Saunderson, et al.2014). ACS accounts for 60% of hospital admission and 85% of deaths in patients aged over 65 years (Roger,et al., 2012). ACS-induced mortality rate in patients aged over 85 years is at least three folds higher than the age group under age of 65 years (Arnold, et al., 2005).

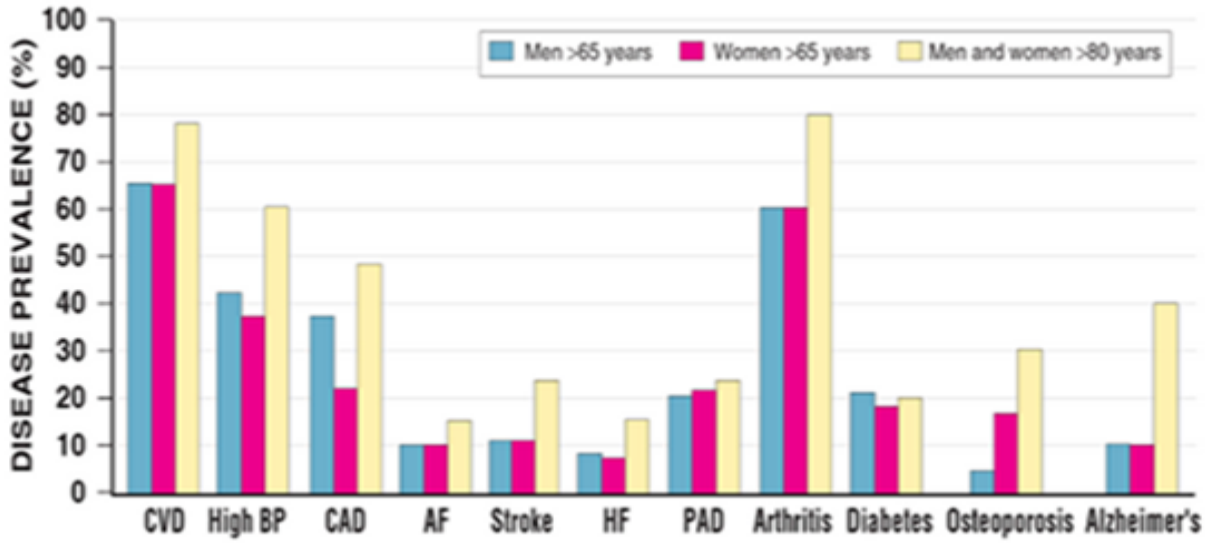

Figure10.Prevalence of current diseases in the united states,data are percentages.AF(Atrial Fibrillation),BP(blood pressure),CVD(cardiovascular diseases),PAD(Peripheral Artery disease),From:Douglas L. Mann,et al.Braunwald's Heart Disease : A Textbook of Cardiovascular Medicine ,2015,ISBN: 978-1-4557-5133-4

Coronary heart disease (CHD) accounts for more than half of all cardiovascular events in both men and women, under the age of 75 in the United States(Lloyd-Jones, et al.,2009). Regardless of race or gender, the elderly will face with significant increases in incidence of CHD with advancing age (WHO,2011).In women compared to men, not only the incidence of CHD takes place 10 years later, but also the occurrence of more life-threatening conditions like sudden death or acute MI delay for at least 20 years(Yusuf, Reddy, Ounpuu, and Anand,2001).

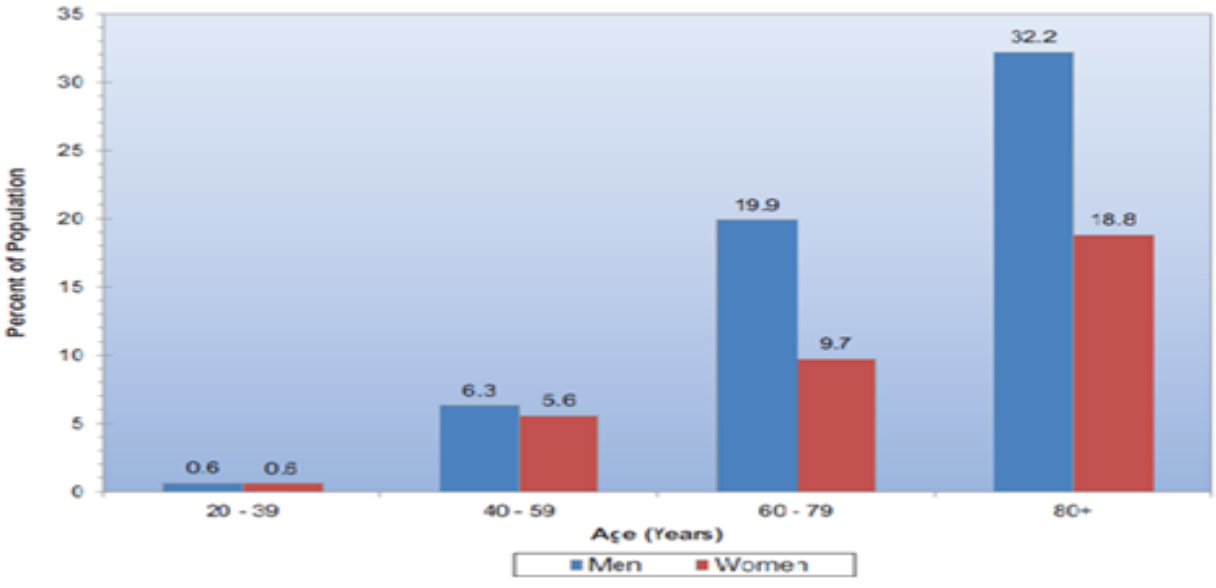

Figure 11.Prevalence of coronary heart disease in the US by age and sex (National Health and Nutrition. Examination Survey: 2009–2012).Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute

AMI is recognized for 40% and 50% of the 17 million annual causes of CVD death in the world (PHIC, 2009; Fitchett, et al., 2011). Advanced age notably associated with increased incidence of AMI. In the USA, more than 60% of hospital admissions are due to AMI in people who are 65 and older(Harman, 1956). Incidence of AMI is increased 10-fold greater in patients 65 to 74 years of age compared to those 35 to 44 years of age, and continuously have higher death rates in patients over the age of 65 years (Hayflick, 1961, Orimo,2006). Up to the age of 80, the prevalence of AMI appears in both sexes in equal frequency, but then it will be more common in women (Roger,2012).

In Canada, ACS is responsible for 19,000 deaths annually, whereas it has been estimated the AMI prevalence is almost 70,000 per year (Welsh, Travers, Huynh, and Cantor, 2009). Among Canadian adults aged 65 to 74 years, the prevalence rates of heart disease have been estimated to be 14.8%, it reaches 22.9% over aged 75 years (Benjamin, 2017; Mozaffarian, et al.,2016).

Mortality of ACS and AMI, in persons who experience it for the first time is estimated 34% and 15% respectively, and it is projected that, every 42 seconds, an American will suffer from MI (Mozaffarian, et al., 2015). Coronary heart disease accounts for 51% of all cardiac death in the USA (NHLBI, 2007).

In 2013, CHD was accounted for one-seventh of all deaths among the Americans. It has been computed that one American is attacked every 34 seconds by acute coronary events and one of these patients dye every 84 seconds (ARIC,2004-2009). With increasing age, the prevalence rate of AMI, appears to be rising, so that in adult aged 65-74 years compared to 35-44 age group, it is approximately seven times higher (Goodman, et al.,2009). The estimated median age at first MI in men and women is 65.1 and 72.0 years respectively (Kolansky, 2009).

The economic burden of acute coronary syndrome in elderly

The impact of age on ACS has made its significant economic burden in elderly [76]. Hospitalization rates for ischemic heart disease are increased with advancing age. ACS as the most common condition related to ischemic heart disease in the USA, is significantly common condition associated with heart disease leading to hospitalization in the USA(PHAC,2009;Yusuf, Reddy,Ounpuu, and Anand,2001;Mozaffarian,2015).In General, the economic burden of ACS has a direct impact in the increase cost of health care. It has been reported the US spends more than 150 billion dollars annually for their total direct medical expenditures(CIHI,2017). It has been shown that the elderly with AMI are the biggest users of professional health services(Maton,1997;Cohen,2014). In Canada, the average cost of AMI in elderly patients, in a 6 year care-period, has been estimated $28,169 per patient (Ross,1993). There is a significant need to distinguish the ACS and AMI utilizing cardiac risk- stratification in order to reduce the cost of the health care system.

Risk factors for acute coronary syndrome

Coronary heart disease is usually caused by atherosclerosis, which creates a plaque resulting from migration and accumulation of macrophages (foam cells) inside arterial walls (chronic inflammatory response(Hansson, and Hermansson, 2011). Atherosclerosis induces intimal smooth muscle cell proliferation (intimal hyperplasia) constructing a bump called atheromatous (fibro-fatty) plaque (Libby, 2002; Lind, 2003). The growing bump on the arterial walls, with decreasing cross-sectional area of the vessels, contributes to partial or complete blockage of the narrow coronary arteries (Wagenknecht, et al., 2009; Kim, et al., 2011), this leads to disturbances in coronary circulation and therefore insufficient oxygen supply to the heart muscle. In other words, the atherosclerotic plaque may develop slowly and encroach into the arterial lumen, or turn vulnerability into thrombosis yielding obstruction.

The established atherosclerotic plaque consists of two main parts (Wang, and Bennett, 2012):

1) A fibrous cap that is composed of vascular smooth muscle cells and their major secretory products (such as collagen and elastin), inflammatory cells (such as macrophages, T lymphocytes, dendritic cells, and mast cells)

2) A "necrotic" core which is surrounded by fibrous cap, and includes intra cellular and extracellular lipids, foam cells, and debris.

A developed atherosclerotic plaque contains high concentrations of calcium salts as well (Roger, et al., 2012).

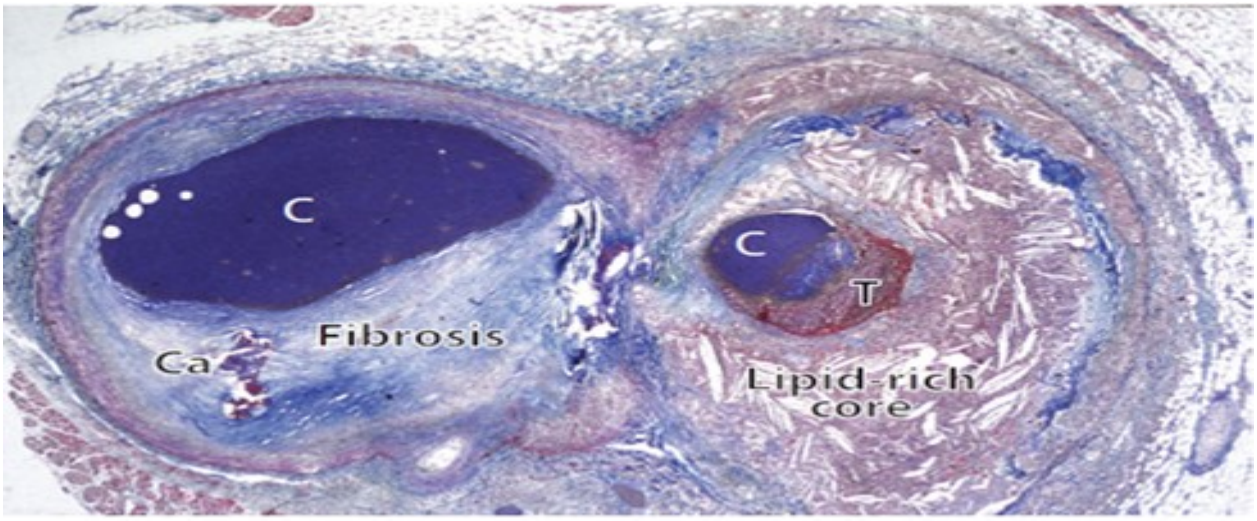

Figure12. A cross-sectional distribution of left coronary artery bifurcation that illustrated severe atherosclerosis. A fibrous plaque in the left circumflex (Left),a complicated plaque with a nonocclusive thrombosis in the left marginal artery, a branch of the circumflex artery which called obtuse branch, (Right).Abbreviations: C:contrast in the lumen, Ca: calcification, T: thrombosis. From: Pierre Théroux, Acute Coronary Syndromes, 2nd edition, A Companion to Braunwald's Heart Disease,2011,C H A P T E R 6,page 42

Although atherosclerosis plaque stability results from cap thickening and inflammation degree of the capsule, plaque instability and or its rupture refers to vascular smooth muscle cell apoptosis, that result in cap thinning, segregation of collagen and extracellular matrix (Eggers,et al.,2008) [as structural and biochemical supporters of surrounding cells].

The vascular endothelium has a crucial role to maintain vascular integrity. Therefore, age associated vascular endothelial dysfunction; vascular stiffness and inflammation contribute to rise in the incidence and prevalence of CHD with advancing age in both sexes(Virmani,et al., 2006). The role of atherosclerosis has been proven over many years in clinical medicine as a single largest suspect and main cause of coronary artery diseases that predispose to death and disability with the passing of time (Berenson,et al., 1998).

It has been demonstrated that there are two different fundamental mechanisms for thrombosis on the plaques as superficial erosion of the endothelial monolayer and deep endothelial fissuring which involves the developed plaque(Bolton, and Rajkumar, 2011).

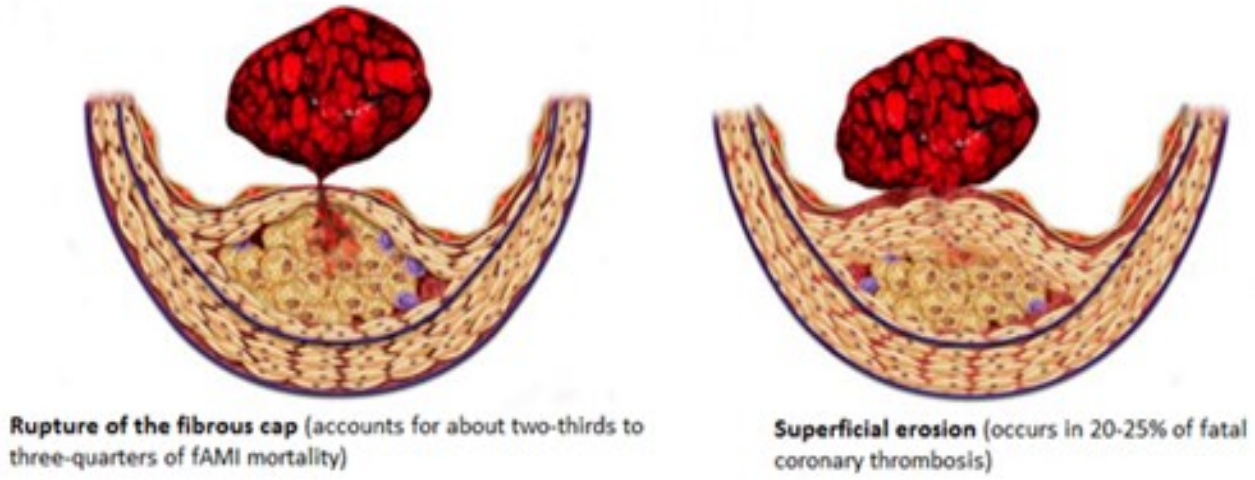

Figure 13. Rupture of the fibrous cap (left) triggers two-thirds to three-quarters of all cases of fatal coronary thromboses. Superficial erosion (right) takes place in one-fifth to one-quarter of fatal coronary thromboses. (Modified from:Libby (2008).The molecular mechanisms of the thrombotic complications of atherosclerosis

Coronary atherosclerosis has been predisposed as an underlying condition that is developing during childhood and adolescence(Maton, et al., 1994). In cardiac myocytes, with developing atherosclerosis, cellular senescence will be observed (Gale, et al., 2011).

As a result, most individuals with age progression have evidence of coronary atherosclerosis. Today, it is well recognized that atherosclerosis has an early and long phase of development, which begins in infancy (Fox, et al.,2005). In other words, ACS in elderly compared to younger counterparts generally has a poorer prognosis (Eagle, Lim, and Dabbous,2004;Rosengren,et al., 2006; Elbarouni,et al., 2009). Moreover, ageing as a verified risk factor has been determined for CHD development that is remarkable to predict short term and long term mortality in the most inclusive of ACS risk models (Wilson, et al.,1998;Gale, et al.,2008;Farhat,et al.,2008;Kozieradzka,et al.,2011).Consequently, it can be deduced that the prevalence of coronary artery diseases increases with advanced age. However, it is now well recognized that among symphony orchestra players that create atherosclerosis, ageing has a non-modifiable role(Niemann, et al.,2011) that makes a prominent ear-splitting noise in this orchestra.

Among the identified atherosclerotic risk factors including: LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, male sex, family history of early MI, diabetes mellitus, and smoking, ageing has a significant rolethat independently promotes the development of atherosclerotic disease even if all other mentioned risk factors could be controlled (Saunderson,

et al.2014,Mueller,1991).Considering that age is included in the main risk-related fashions, consequently older people are put as high risk based on age alone (Naylor,2003).

Biomarkers of acute coronary syndromes in the elderly

Biomarkers or biological markers are defined as cellular, biochemical, molecular or anatomic modifications that are empirically measurable in order to detect the process related to normal or particular health conditions. These tests can assist in understanding the evolution of diseases, risk factors of diseases, monitoring responses to therapeutic interventions in a culture medium such as blood serum or tissue extract (Abernethy, et al., 2001, Morrow, & De Lemos, 2007; Wallace, et al., 2008). In other words, in clinics, the use of biomarkers are a practical and dynamic approach in order to study the disease characteristics with referring to screening, diagnosis, prognosis and monitoring medical interventions.

The characteristics of an ideal biomarker for acute coronary events

There has been serious debate among researchers, clinical chemist and physicians to introduce advanced screening strategies. In order to identify patients who are initially free of CHD manifestations but at risk of acute coronary events, the clinicians require safe, accurate, affordable, and reliable biomarker.

A novel and standard cardiac biomarker has to be measured easily, with added new information that can be useful in patient management (Rosalki, 2004). In addition, the main feature of each biomarker has to consist of a release kinetic model from specialized or individual cells, i.e. with specificity and sensitivity.

According to the FDA (Food and Drug Administration) (Lippi, 2015), the feature of an ideal cardiac marker is as follows:

1. Specific:
    - high serum ratio in myocardium
    - not even pathologically found in non-cardiac tissue
    - Show appropriately a clear distinction for different pathogenesis of cardiac involvement (acute to chronic, necrosis, hypertrophy, rhythm)
2. Sensitive:
    - Zero measurement baseline (standard)
    - indicator of early onset and reversible cardiac injury
    - instantaneous release if there is an injury
3. Predictive:
    - Long serum half-life in circulation (indicates that it is reversible)
    - degree of release is proportional to degree of injury
4. Performance:
    - must be accurate, simple, inexpensive and fast detection in all clinically relevant markers

5. Provide a clinical and paraclinical bridge

6. Readily available and noninvasive

History of cardiac biomarkers,from past to present

Despite the fact that there has been a great biomedical debate for decades over the ACS diagnosis (Dolci, & Panteghini, 2006)**,** the acceleration of cardiac biomarkers development has come to an almost complete agreement to introduce a relatively perfect cardiac biomarker (LaDue, Wroblewski, & Karmen, 1954; Karmen, Wroblewski, & LaDue, 1955).

Traditional cardiac biomarkers of acute coronary syndromes

The primary biomarkers applied to identify acute cardiac ischemia consist of aspartate aminotransferase and lactate dehydrogenase isoenzymes.

1. ***Aspartate aminotransferase (AST)***

In 1954, aspartate aminotransferase (AST) or serum glutamic oxaloacetic transaminase (SGOT) was presented as first cardiac biomarkers to determine predictors of coronary events (Henry, Chiamoril, Golub, Berkman, 1960;Wilkinson, Baron, Moss, & Walker, 1972), technically improved in years later (Cabaud, Leeper, & Wroblewski, 1956; Wroblewski, Ruegsegger, & Ladue, 1956), and for many years, that played the most important role to predict acute coronary events (Ruegsegger, Nydick, Freiman & Ladue, 1959;Ladenson, 2007). Increased AST levels can be observed 3–4 hours after acute coronary injury in circulation provides the maximum blood levels in 15–28 hours and then returns to normal levels during 5 days(Wroblewski, 1955). Although AST has a great sensitivity to detect acute coronary injury, it is not an ideal cardiacbiomarker due to its existence in the liver, skeletal muscles, brain and kidneys, that gives significantly a low specificity (Lee, 1986, Saunderson, 2014).

2. ***Lactate dehydrogenase (LDH)***

Elevated level of lactate dehydrogenase (LDH) and its isoenzyme (LDH-1) have been demonstrated among patients with AMI(Rozberg, 1962; Penttilä, et al., 2000), in 1956. Increased blood level of LDH and LDH-1(LD-1) are observed 5–10 hours after AMI, reaches maximum at 2.5 to 6 days and returns to baseline in 12 days (Blomberg, Kimber,& Burke, 1975).

3. ***Creatine Kinase (CK)***

In 1960s, the Creatine Kinase (CK) presented as a better cardiac specific marker to confirm acute myocardial damages (Ishikawa, Saffitz, Mealman, Grace, Roberts, 1997). CK, as a dimeric molecule, consist of two different subunits known as M and B, which split into three distinct isozymes as CK-MB (found predominantly in myocardium), CK-MM (found predominantly in skeletal tissue), and CK-BB (found predominantly in the brain tissue) (Adams, Abendschein, & Jaffe, 1993). It has been determined that the release of CK-MB is particularly obvious following myocardial necrosis (not under ischemic condition)(Wu, 1998), so it was most commonly applied in identifying myocardial injury. It can be typically detected in circulation 3–6 hours following the onset of acute myocardial necrosis, reaches its maximum in 12-24 hours and begins to return to normal level within 48-72 hours (Galarraga, 2003). Although sensitivity of CK-MB is high enough, its extensive tissue distribution will strongly yield poor specificity. In other words, CK-MB elevated levels could be observed in various forms of musculoskeletal damage or myopathies, diseases of small bowel, uterus, prostate, and diaphragm, renal failure, hepatobiliary system disease, non-cardiac surgery, chest trauma, asthma, pulmonary embolism, head trauma, hyperventilation, hypothyroidism, during peripartum period and in substance abuse like cocaine and alcohol (WHO, 1979; Lee, 1987). Consequently, it has been suggested that in order to improve CK-MB specificity, calculating CK-MB relative index as CK-MB/total CK, whereas the ratio greater than 2.5 will be associated with myocardial injury (Mair, et al., 1992).

Thus, the World Health Organization (WHO) confirmed the use of serum AST, LDH, CK, and CK-MB levels in presence of clinical and electrocardiographic manifestations to identify acute myocardial infarction, in 1979(WHO, 1979).

4. ***Myoglobin (MYO)***

Myoglobin (MYO) was introduced as a primary indicator of myocardial damages in 1978(Kolendorf, Pedersen, Christiansen, & Gad, 2009). It is a globular oxygen-carrying protein which found in myocardial tissue and striated skeletal muscle (Ohman, et al., 1990). The first report was published in 1975, confirmed the association between elevated serum levels of MYO and AMI (Varki, Roby, Watts, & Zatuchni, 1978). Myoglobin can be detected within 1 hour after the initiation of myocardial necrosis, reaches its maximum in 4-12 hours and returns to normal level within 24-36 hours (Ebashi, 1963). A high concentration of myoglobin in skeletal muscles is the reason why MYO has a poor specificity (Galarraga, 2003;Jaffe, 2012). In other words, though myoglobin is one of the earliest serum markers for AMI, there are various medical

conditions that could increase myoglobin blood levels in the absence of acute coronary occlusion.

5. Cardiac troponin(cTn), as a biomarker in the current standard of care

In 1963, it was revealed that a new myofibrillar protein called troponin is integral to muscle contraction in skeletal and cardiac muscle and absent from smooth muscle(Takeda, Yamashita, Maeda, & Maeda, 2003).

Biology of the Troponin Complex in Cardiac Myocytes

Troponin is a complex of three subtypes (Katus, Remppis, Scheffold, Diederich, & Kuebler, 1991): Troponin I (Tn I) which binds to actin with Inhibitory role, Troponin T (Tn T) which binds to tropomyosin, Troponin C (TnC) which binds to calcium ions and all of them are located on the actin filament in sarcomere.

Sarcomere is the basic contractile unit of muscle cell composed of thin ball shaped filament, called actin, and thick filament, called myosin, includes tail, hinge and head as dual- golf club shaped. Each muscle fiber or myofibril (a long, cylindrical, multinucleated cell) contains hundreds of sarcomeres (Brogan, et al., 1997).

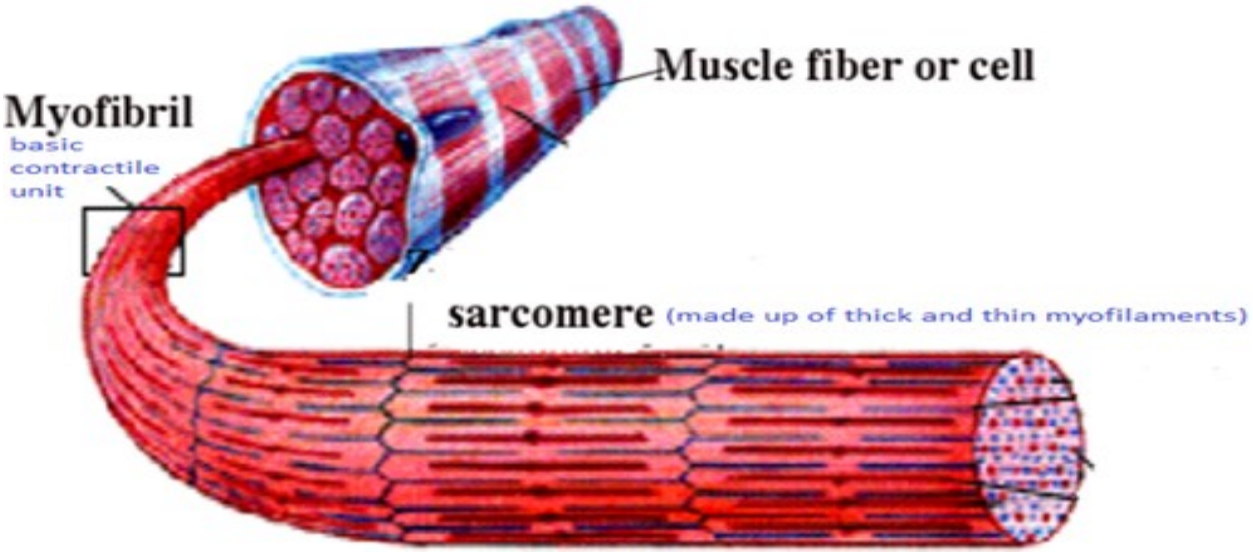

Figure 14. Structure of musculoskeletal contractile cell (Modified from: Marieb,et al.,2010). Anatomie et physiologie humaines)

Tropomyosin attaches longitudinally to the actin filaments. Each actin molecule has a myosin-binding site. If calcium ion is unavailable, the binding site of myosin to actin will be blocked by tropomyosin-troponin complex.

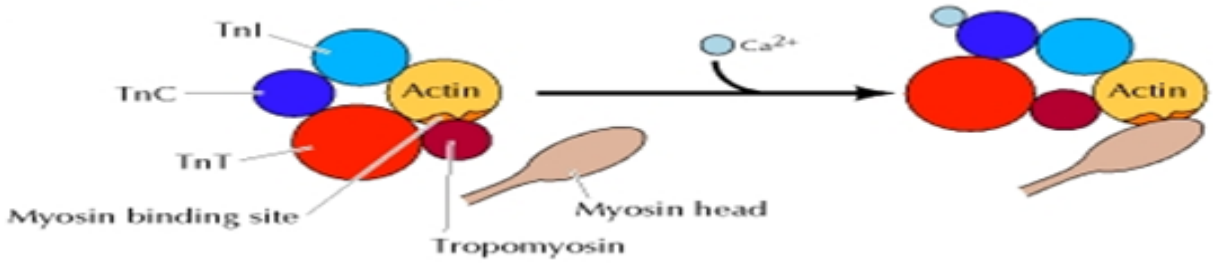

Figure 15. A schematicview:Tropomyosin binds lengthwise along actin filaments and, in striated muscle, is associated with a complex of three troponins: troponin I (TnI), troponin C (TnC), and troponin T (TnT). In the absence of Ca2+, the tropomyosin-troponin complex blocks the binding of myosin to actin. Binding of Ca2+ to TnC shifts the complex, relieving this inhibition and allowing contraction to proceed. (Cooper, G. M., & Hausman, R. E. (2009). The cell: a molecular approach. Washington, DC: ASM Press; Sunderland, MA: Sinauer Associates, c2009.)

By binding of calcium ion to the troponin C, tropomyosin moves to lateral side, that causes exposed binding side on actin for myosin(dark area), then, results from ATP-hydrolysis, some changes occurs in myosin head that promote to bind myosin head into exposed site(Figures 15 &16)

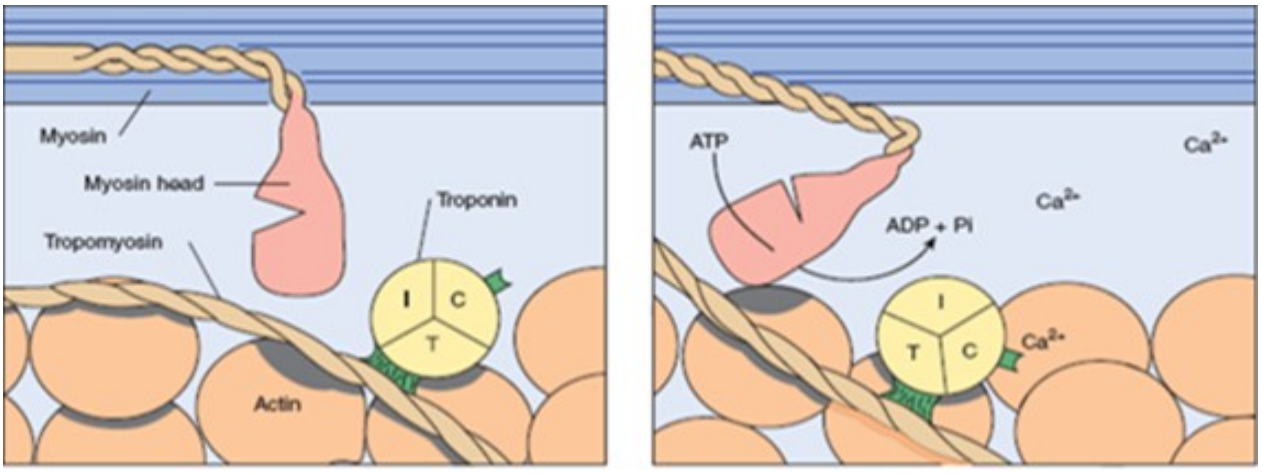

Figure 16. Interaction between the actin and myosin filaments ,from:In Fuster, V., In Harrington, R. A., In Narula, J., & In Eapen, Z. J. (2017). Hurst's The Heart, 14e. New York, NY: McGraw-Hill Education LLC

It has been assumed that in addition to the structural sources of troponin, there is at least one other pool that is called cytosolic pool (Wu, 1998; Thygesen, 2010).The cytosolic or early releasable pool for cTnI and cTnT accounts for almost 3.7% (Wu, 1998) and 5% (Thygesen, 2010) of total released troponin respectively. Consequently, it may justify the long persistence of cardiac troponins in blood circulation following an AMI. Besides, cytosolic pool is responsible for the biphasic kinetics of troponin as a rapid release of free cytoplasmic troponin and then a gradual structural troponin release(Sribhen, Phankingthongkum, & Wannasilp, 2012).

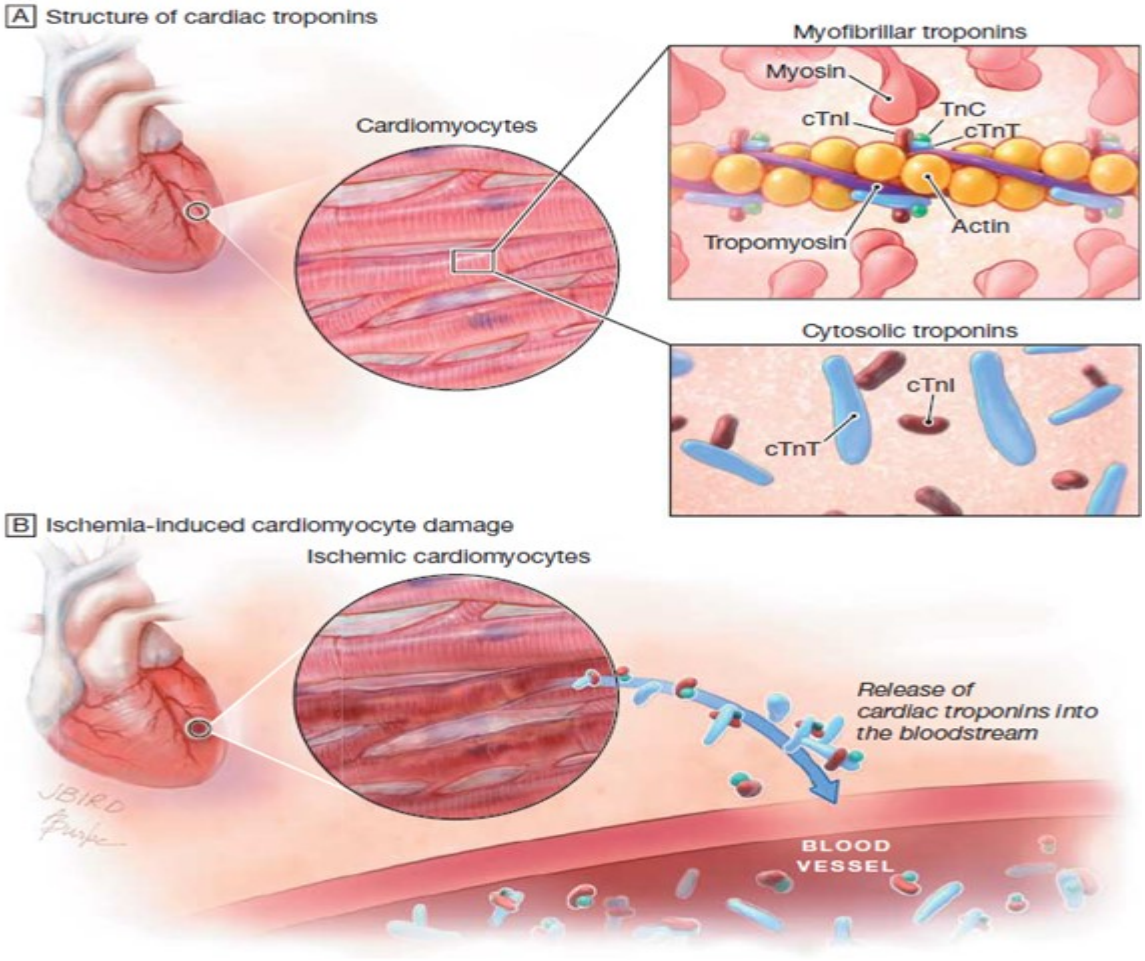

Figure17. Mechanism of release of cardiac troponin after ischemic cardiac injury, available at: http://ja.ma/1NKufTm #AMI #heart attack)

Although the biochemical behavior of cTnI is quite clear, that means, cTnT has never been detected neither during neonatal development nor in pathologic conditions of all the organs and body tissues, except the heart (Tiwari, 2012), the situation of cTnT becomes more complicated.

Apparently, the elevated levels of cTnT are detectable in some patients who suffer from musculoskeletal disorders or renal failure (Tucker, 1997). Therefore, cTnT could be prone to false-positive elevation in the absence of significant coronary artery disease.

Elevated levels of cTnT and cTnI are detectable within 3-4 h after of the onset of ischemia and typically reach its maximum after 12-48 h (Bertinchant, 1996) and stay elevated for 4-10 days that refers to a gradual decline in myofibril-bound troponin complex (Jaffe, 2011;Twerenbold, 2012). Cardiac troponin assays are based on high-affinity antibodies thatare specific for both cTnT and cTnI, but because of the uniform amino acid sequences of troponins in both myocardial and musculoskeletal origins, measuring cTnC has not been proposed (Tiwari,2012).

Novel high-sensitivity cardiac troponin assays (hs-cTn), compared to previous generation, in order to detect myocardial necrosis with respect to their sensitivity have been developed (Jaffe, 2011; Twerenbold, Jaffe,Reichlin, Reiter,&Mueller, 2012).Hs-cTn assays provided an opportunity to detect cardiac troponin levels which is 10- fold lower in previous assays, hence they are able to measure the lowest troponin values in healthy individuals (Apple, & Collinson, 2011). Each assay has a unique, incomparable and assigned cut off value that refers to the dissimilarity of the antibodies and the different matrix compositions of the assays (Ferrieres, 1998; Perry, 1999; Panteghini, 2001). In addition, the various components of circulating troponins are distinguished by various assaysin different ways (Venge, Johnston, Lindahl, & James, 2009). Furthermore, cardiac troponin can be detected by the new highly sensitive assay in healthy individuals that indicates unique variation inside or interindividuals that could refer to a normal cardiac cells turnover or an unidentified mechanism (Sandoval, & Apple, 2013; Thygesen, Alpert, Jaffe, & White, 2015,).

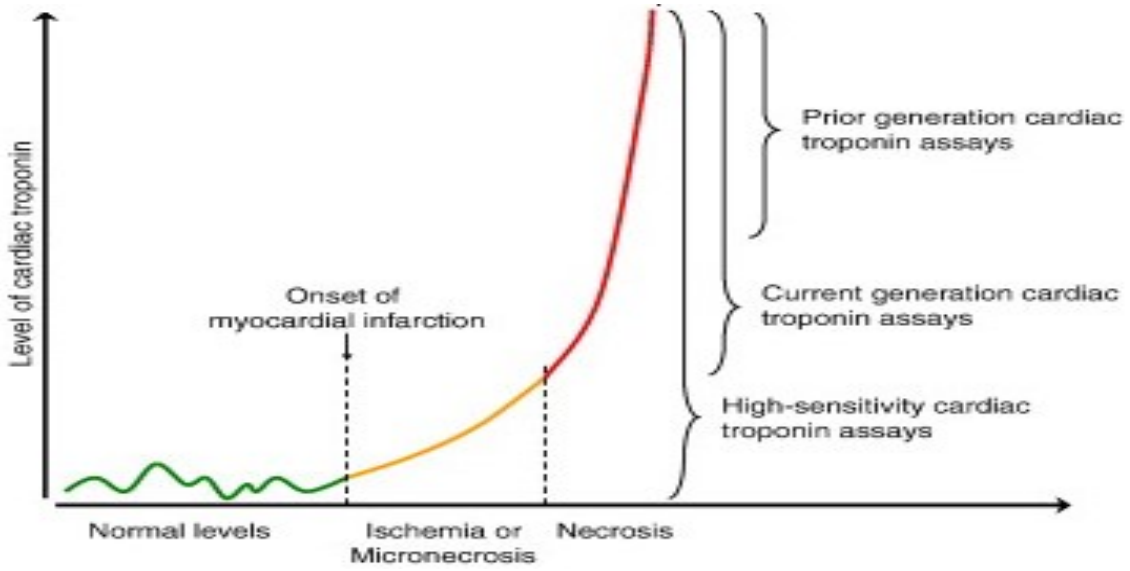

Figure 18, Detection range of various cardiac troponin assays (from Hochholzer et al. Am Heart J 2010).

The green line refers to normal turnover of cTn in all human beings. The orange line refers to a slight but rapid increase of cTn that reflects either an early-release of cytosolic pool of cardiac troponin or myocardial microinfarction.The red line represents a steep rise in cTn levels, 2 -6 hours after extensive myocardial infarction. In addition to elevated cardiac troponin monitoring, hs-cTn assays are designed to detect lower levels of troponin caused by ischemia/micro necrosis and the normal turnover as well. While the first generation of cardiac troponin assays only detect a significant increase of cardiac troponin.

Although increased serum troponin level is defined as the value of 99th percentile upper reference limit (URL) by including 99% of all troponin values of the given population (Apple, & Collinson, 2014), URL values for the same assay could vary significantly in different reference groups (Clerico, et al., 2008,Olivieri, 2012).Cardiac troponins assays would be considered as highly sensitive tests if: their coefficients of variance are less than 10% at the 99th percentile value of the healthy reference population, and the concentrations above the test detection limit can be measured in more than 50% healthy population. (Olivieri, 2012).

Behavior of troponin in the elderly

Both age and gender significantly have an effecton hs-cTn assays (Missov,& De Marco, 1999;Olivieri,2012), as it decreases in women and increases with advancing age, this may be due to the myocardial ageing, in both sexes, particularlyageing causes a remarkable increase of

serum troponin. Consequently, the interpretation of serum troponin in elderly, exceptionally in old-old with presence of comorbidities needs further consideration.

Sensitivity and specificity of troponin

Although the interpretation of diagnostic tests is a clinical process that have own lexicon with regards to its science, the efficiency of a laboratory test is usually presented in terms of sensitivity and specificity.

Both cardiac troponin T and I isoforms are distinctly found in myocardium (Jeremias, 2010),so it is a cause of high cardiac specificity for both of them. It is hypothesized that the normal baseline troponin values should be 0.1–0.2 ng/L, caused by persistent loss of cardiomyocytes throughout life (Panteghini, Pagani, & Bonetti, 1999).Despite the cardiac troponins sensitivity and its predictive value have improved over time, its specificity does not change notably over time (Balk, 2001).

Sensitivity of cTnT in hospital outpatients varies between 25-65 percent (time zero), increments to 59-90 percent at 2 to 6 hours after their admission, and reaches 100 percent within 6 to 12 hours after admission (Bertinchant,1996;Eggers,, Nordenskjöld, & Lindahl, 2004;Jaffe, Babuin, Apple,2006). For cTnI, its sensitivity in time zero is at most 45 percent, increases to 69–82 percent at 2 to 6 hours after admission, and the same as cTnT, achieves to 100 percent within 6 to 12 hours after admission (Eggers, Oldgren, Nordenskjöld, & Lindahl, 2004;Jaffe, Babuin, Apple,2006;Twerenbold, Jaffe, Reichlin, Reiter, & Mueller, 2012). As a result, the maximum sensitivity of cTn assays could be observed longer than 6 hours after myocardial cell death occurs (Christenson, 2007; Hammarsten, 2012). Thus, it is recommended to measure cTn blood levels at time zero and at least 6-9 hours after patient admission in order to improve the accuracy of the diagnosis of myocardial infarction (Koerbin, Tate & Hickman, 2010).

The positive predictive value, for cTnI, at time zero and 12 hours after admission is estimated to be 25% and 89% respectively, whereas for cTnT, is estimated to be 35% and 57% respectively (Twerenbold, , Jaffe, Reichlin, Reiter, & Mueller, 2012). The negative predictive value of cTnI at time zero and 12 hours after admission is predicted to achieve 85% and 98% respectively, whereas for cTnT, it is estimated to be 88% and 99% respectively(Twerenbold, , Jaffe, Reichlin, Reiter, & Mueller, 2012).

The specificity of cTnI and cTnT has been reported to be in the range of 83 - 98 percent and 86–98 percent respectively (Twerenbold,et al., 2012).

Although few studies have been reported that the level of cTn is increased with advancing age (Ferri, 2010;Reiter, Reichlin, Twerenbold, & Mueller, 2011;Anderson, 2011), reasons of which still remains obscure, even with explanations like presence of more comorbidities or silent heart diseases in elderly, and age dependent phenomenon. In other words, the troponin alterations in elderly, particularly among the old-old, are not inclusive.Emerging serum cardiac biomarkers is summarized in following graphs in the first hours (figure 19) and days (figure 20) after the onset of acute myocardial infarction. High-sensitivity assays are capable of detecting cTn in blood circulation more accurately even at a concentrations 10 times lower than conventional assays (Liu, et al,2017).Therefore, use of high sensitivity assays of troponin could reduce the risk of being misdiagnosed with ACS compared with conventional assays.

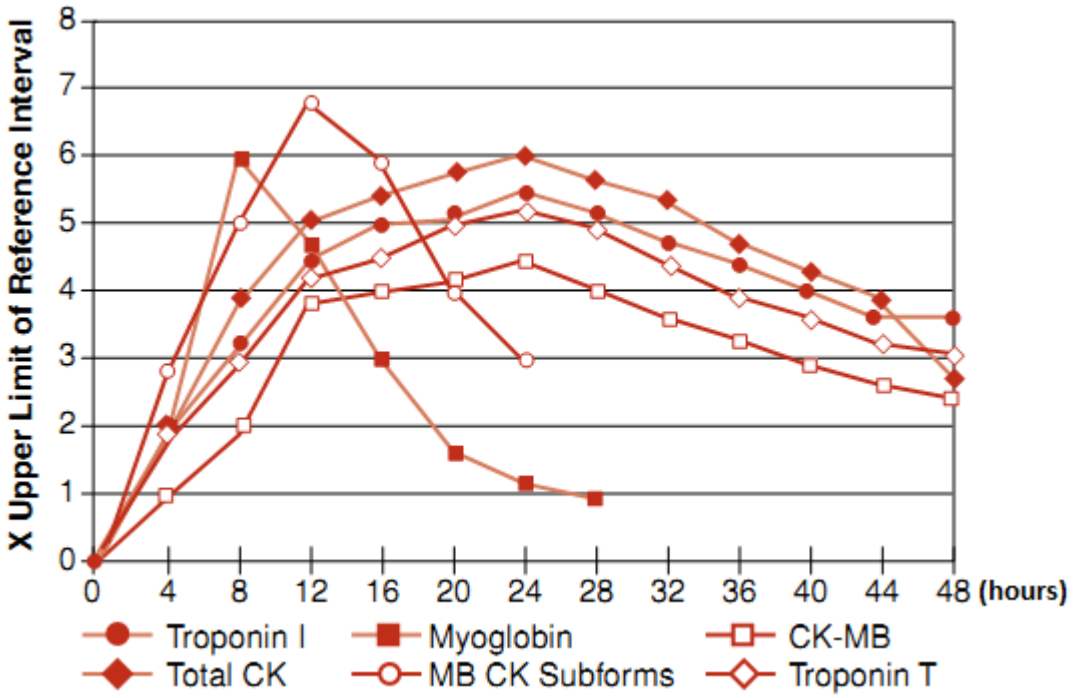

Figure 19.Time courses (hours) for elevation of various biomarkers after the onset of symptoms of AMI.(Source : Michael L. Bishop, et al. Clinical chemistry, 6th edition, 2010, chapter 25, cardiac function, page 551, ISBN 978-0-7817-9045-1)

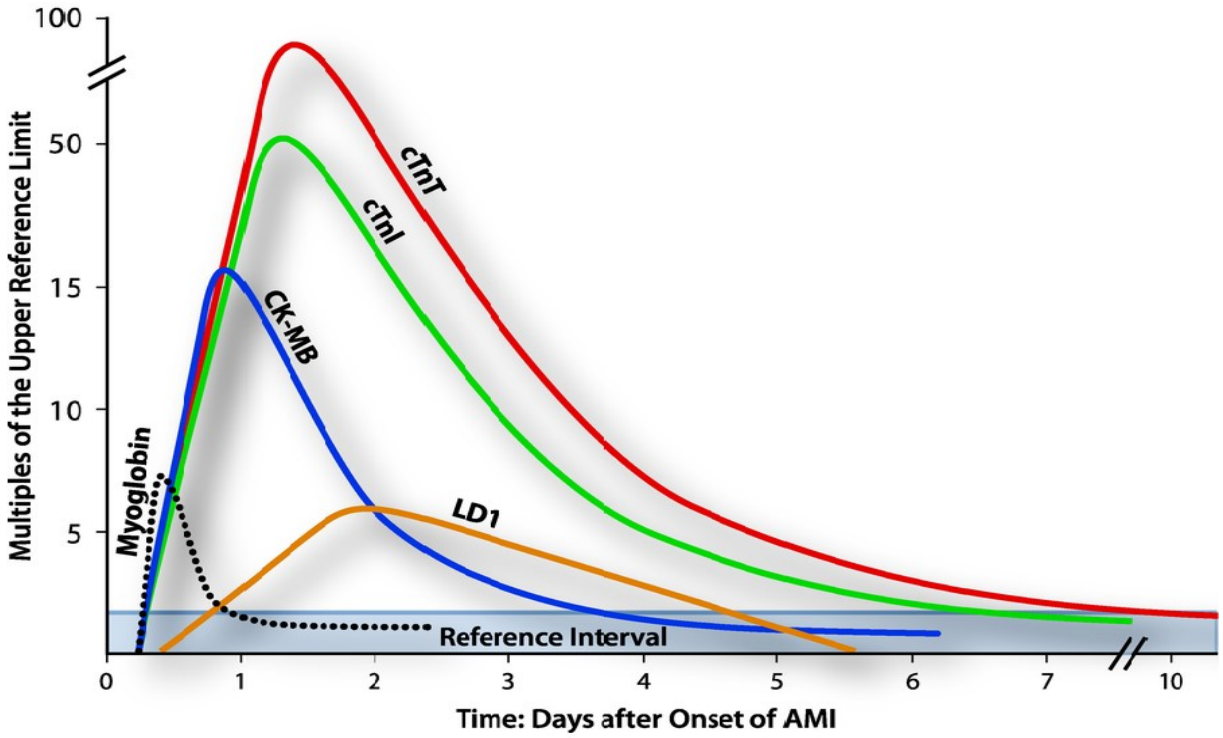

Figure 20.Time courses (days) for elevation of various biomarkers after the onset of symptoms of AMI. Reprinted from:Goodier, J. (2009). Lippincott Williams & Wilkins anesthesiology, creatine kinase-MB to troponin: the adoption of a new standard.

As it is explained, reference values for cardiac troponin encompass the values of 99% of a healthy population, the results vary between different laboratories, so at present, there is still no certain standard consensus on which cut-off point value should be used (Jaffe,2000).The baseline of troponin level has been suggested as 0-0.4 ng/ml (negative), 0.05-0.49 ng/ml and ≥0.05 ng/ml for intermediated risk and strong risk of acute myocardial infarction respectively (Lippi, Sanchis-Gomar, & Cervellin,2016).

In conclusion, to this date, among available cardiac biomarkers, cardiac troponin is the biomarker of choice to detect acute coronary events (Sanchis-Gomar, Perez-Quilis, Leischik, & Lucia, 2016).

Causes of increased cardiac troponin values

Although cardiovascular disease (CVD) has been defined as a group of diseases that involve both the heart and blood vessels(Fitchett, et al.,2011),at some point, there is an ambiguity in defining its related-conditions such as coronary heart disease (CHD), coronary artery disease (CAD), and acute coronary syndrome (ACS).

CHD refers to heart diseases such as angina pectoris, MI and silent myocardial ischemia, but CAD typically apply to indicate pathologic changes in the coronary arteries that usually caused by atherosclerosis. In other words, CAD is a condition which characterized by atherosclerosis in coronary arteries, could refer to pathologic process and can remain symptomless (Lippi, & Cervellin, 2016). Instead, ACS nearly always becomes symptomatic and it is a life threatening condition, irrespective of the presence of CAD (Roffi,2015).

There are different approaches to classify the clinical conditions other than myocardial infarction that cause cardiac troponin to rise. One of the more detailed classifications related to cTn increase is presented as (Apple, & Collinson, 2014):

1. Troponin leak primary to myocardial ischemic injury: Plaque rupture, Intraluminal coronary artery thrombus formation

2. Troponin leak secondary to myocardial oxygen supply-demand imbalance: tachy-/brady-arrhythmias, aortic dissection or severe aortic valve disease, hypertrophic cardiomyopathy, shock (cardiogenic, hypovolemia, or septic), severe respiratory failure, severe anemia, hypertension with or without left ventricular hypertrophy, coronary spasm, coronary embolism or vasculitis, and coronary endothelial dysfunction without significant CAD

3. Troponin leak not associated with myocardial ischemia: cardiac (contusion, surgery, ablation, pacing, or defibrillator), shocks, rhabdomyolysis with cardiac involvement, myocarditis, cardiotoxic agents (e.g. Anthracyclines, Herceptin)

4. Multifactorial or undefined myocardial insults: heart failure, stress (Takotsubo) cardiomyopathy, severe pulmonary embolism or pulmonary hypertension, sepsis and critically ill patients, renal failure, severe acute neurological diseases (e.g. stroke, subarachnoid hemorrhage), Infiltrative diseases (e.g. amyloidosis, sarcoidosis), strenuous exercise

Consequently, detection of elevated serum concentrations of cardiac troponin (>99th percentile URL) in the presence or absence of ischemic heart disease symptoms, or other diagnoses associated with myocardial damage have to be ruled out.

Acute Coronary Syndromes (ACSs)

ACS - as a subset of CHD addresses a range of conditions that are compatible with unstable angina (UA), non ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) - causes a decrease levels in coronary artery blood flow (Bertrand, 2002).

As discussed above, the underlying etiology of ACSs is the atherosclerosis, which is characteristically composed of a vulnerable plaque with a thin layer of fiber and a large lipid core. Sooner or later, this plaque tears, causes platelet accumulation and activation, which lead to coronary thrombus formation, narrows the coronary arteries and ultimately reduces the flow of oxygen-rich blood to the section of heart muscle that is fed by the coronary artery.

It can be difficult to distinguish UA from NSTEMI (Mega, 2005). UA is defined as myocardial ischemia that occurs at rest or even with slight physical exertion without any presence of cardiomyocytes necrosis, so that is distinguishable from NSTEMI by the pain frequency-severity-duration to cause myocardial necrosis (Cannon, 1997). ECG findings associated with UA can be found in 30-50 percent of the patients, including normal morphology, ST-segment depression, T-wave inversion, or due to a combination of all these factors, may vary depending upon the severity of clinical presentations (Ottani, 1999, Antman, 2004). Although small amounts of cTn could be traced in the serum of patients suffering from UA, it has not been shown any prognostic value in predicting future coronary events (McCarthy,, Wong, & Selker, 1990).

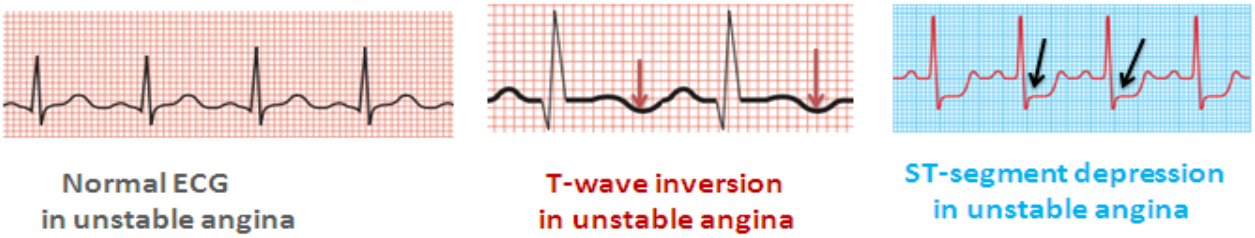

Figure 21. ECG of unstable angina, (available at: http://nstemi.org/unstable-angina/, accessed: July 5, 2017)

STEMI is typically the result of an acute and sudden complete interruption of blood flow to part of the myocardium which could be displayed as an unusual pattern by ECG with ST-segment

elevation, whereas NSTEMI mostly results from a partial occlusion which develops to become total blockage of coronary artery as well, but does not exhibit ST segment elevations in ECG(Figure 22). STEMI is the most severe type of ACS with the highest mortality rates (Goodacre, 2002).

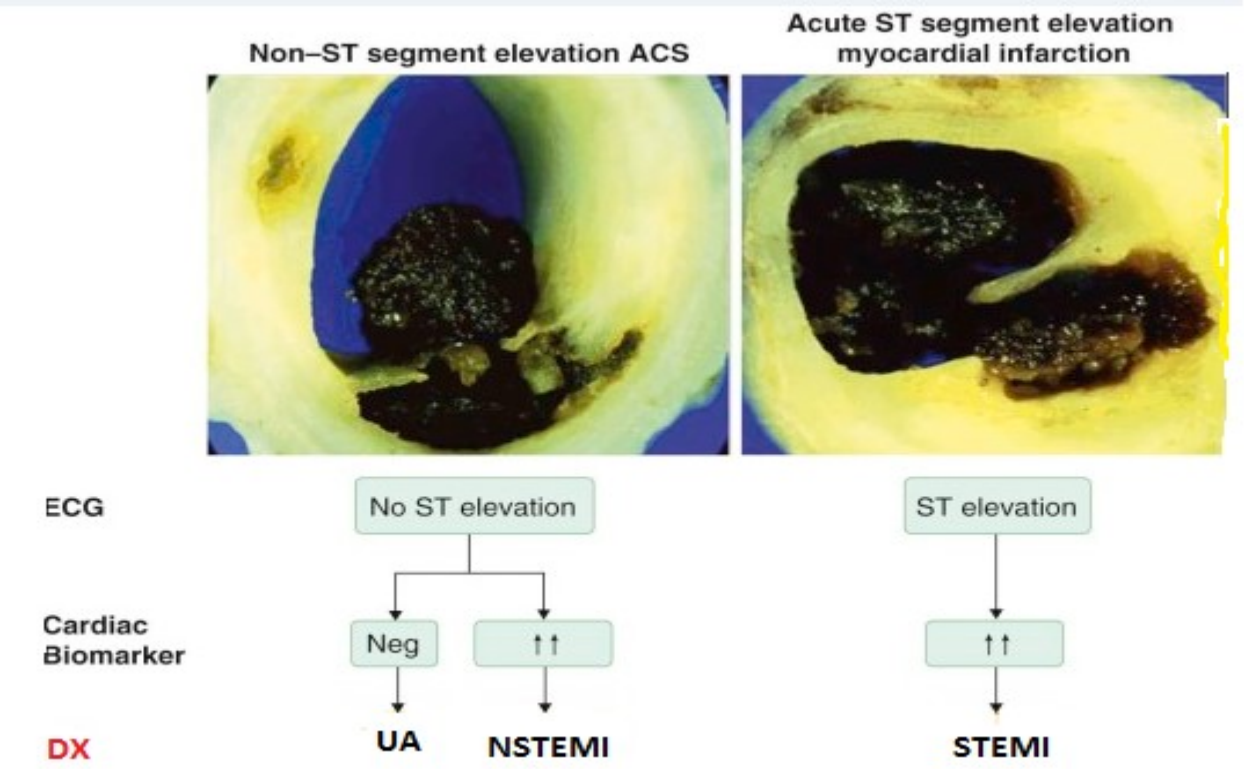

Figure 22. Acute Coronary Syndrome, unstable angina and non-ST elevation myocardial infarctionModified from: Ange, R. A., & Hillis, L. D. (2015). Acute Coronary Syndrome. Goldman's Cecil Medicine. Acute Coronary Syndrome, unstable angina and non-ST elevation myocardial infarction, Goldman-Cecil Medicine, pages 432-440

Main clinical presentations

A typical symptoms of ACS include chest pain (most common), referred pain (arm, the jaw, the neck, the back, or the abdomen), nausea, vomiting, dyspnea (may be as a sudden onset), diaphoresis, light-headedness (Alexander, 2007). Referred or radiating pain to the shoulder, left arm, or both arms may increase the probability of ACS (Avezum, 2005).

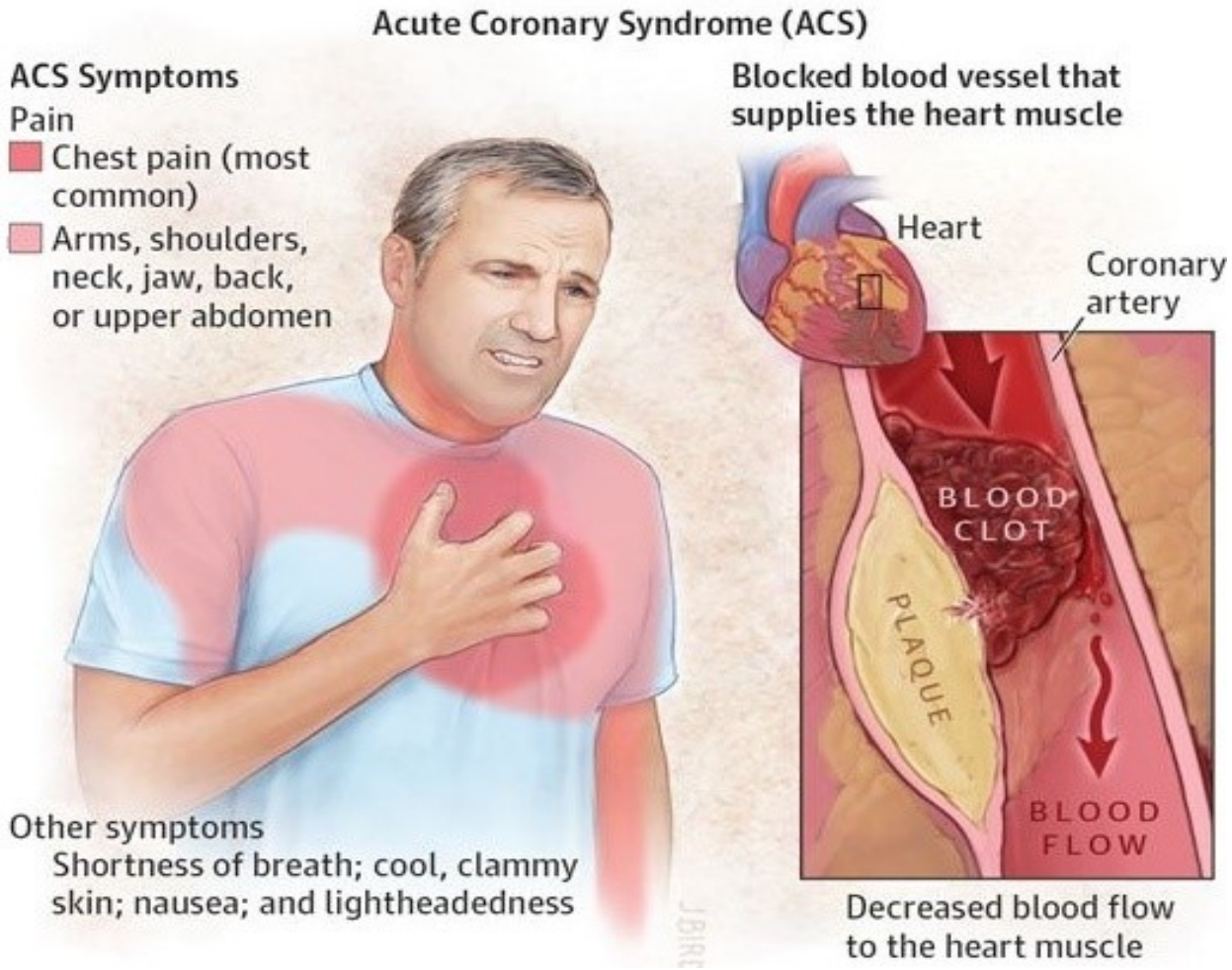

Figure 23. Chest Pain and Acute Coronary Syndrome,Reprinted from:https://jamanetwork.com/journals/jama/fullarticle/2468893

Diagnostic evaluation

The main step for assessment of a patient with ACS is to distinguish the probability of coronary-artery disease as causing any symptoms. The American College of Cardiology/American Heart Association (ACC/AHA) proposed guidelines include, among the factors associated with the high probability of ACS, prior history of angina, AMI or CHF, History of established CAD by angiography, new ECG changes, and elevated cardiac biomarkers (Jaffe, et al.,2000).

Identification of ACS in older patients

Seniors often experience a different range of symptoms, so the diagnosis of ACS among them is challenging. Although chest pain is still the most frequent symptom in older patients, autonomic

symptoms such as syncope, malaise and confusion can be the only presenting symptom of ACS among elderly (Elbarouni, et al.2009). Not only electrocardiogram includes the relatively high prevalence of disturbances such as left bundle brunch block or left ventricular hypertrophy, but also increased troponin levels may be affected by comorbidities such as diabetes or renal failure (Twerenbold, Jaffe, Reichlin, Reiter, & Mueller, 2012). Additionally,more than two out of five ACS patients are aged 85 years or over do not present diagnostic ECG abnormalities compared with a quarter of those under 65 years (Veerasamy, et al.,2015).Moreover, in elderly, NSTE-ACS instead of STEMI is frequently observed (Alpert, Thygesen, Antman, & Bassand, 2001; Storrow, Lardaro, Alexander, & Apple, 2013).

Consequently, this significant age -related characteristics of ACS in elderly patients could lead to uncertainty in initial diagnosis or misdiagnosed on admission and treatment in a timely and accurate fashion.

Acute Myocardial Infarction (AMI)

AMI definition refers to cardiomyocytes necrosis from a sudden and a prolonged ischemia during the course of events in acute coronary syndromes in subsequent development of atherosclerosis (Higgins, & Higgins, 2003). Advanced age as an established risk factor is one of the leading cause of formation and progression of atherosclerotic plaques. Currently, due to extensive use of cTn, AMI definition has been turned from a clinical diagnosis that was made on the basis of ECG findings and biomarkers blood levels to a laboratory measurement of cTn which is supported by clinical and ECG findings (Nguyen Dang, Karlsson, & Herlitz, 2016).

Acute myocardial damages lead to a biphasic rise of serum troponin levels that resulted from the primary release of cytosolic pools and then from myofibrillar structural sources [141,194]. Detection of the increase and /or decrease of cardiac troponin is the principle of consensus in new definition of MI, along with one of the myocardial ischemic symptoms, ECG disturbances and cardiovascular diagnostic imaging tests that appear a new regional loss of viable myocardium, and recognition of occlusive intracoronary thrombus at autopsy(Apple, & Collinson, 2014).

AMI in the elderly

In older patients with AMI, not only the presence of atypical symptoms is more frequent, but also the elderly patients compared to the younger patients are exposed to a higher mortality rate (Rittger, 2011, Banach,2005). Furthermore, in elderly patients with AMI, both perception and location of ischemic pain maybe changed (Yarzebski, Goldberg, Gore, & Alpert, 1994). They

may describe their complaints as autonomic symptoms such as dyspnea, syncope, shoulder or back pain, weakness, fatigue (in women), acute confusion or altered mental status (particularly if the patients aged over 85 years(Roberts, & Kleiman,1994),epigastric discomfort and even could be described by concurrent disorders. In addition, pre-hospital delay in the elderly patients with AMI has been reported frequently, that could be related to atypical chest pain, diminished chest discomforts, cognitive impairment, comorbidities, or social restrictions (Han, et al., 2007).

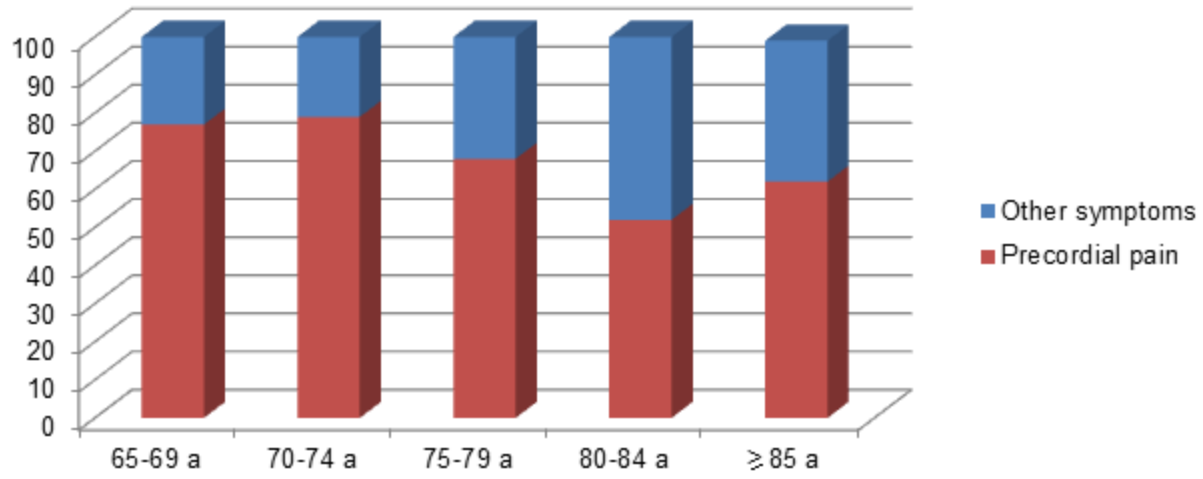

Figure 24. Presentation of AMI according to patient age.Precordial pain is decreased with advancing age. Reprinted from: Bayer, Chadha,Farag, & Pathy, 1986)

Scope of the Problems

As aforementioned, there is often an interaction between the physiological processes of aging and age-related pathological processes in the cardiovascular system. Thus, in age-related cardiovascular diseases, aging may alter the clinical manifestations, responses to treatment, and outcomes of ACS or AMI. As a result, clinical standards have to be in accordance with age, if not, they may not be applicable to different age groups. Older patients with acute coronary events may present with atypical symptoms, so elderly patients could benefit more from laboratory methods, like hs-cTn, than younger patients. On the other hand, it has recently been reported a great possibility of false positives for hs-cTnT assay in elderly patients with AMI (Ferri, 2010). The major conflict in elderly patients, particularly those 80 years of age and older is the lack of reliability of diagnostic characteristics such as chest pain, electrocardiography, and interpretation of biomarkers, in order to exclude AMI (Barron, et al., 1998). Further, positive

predictive value of chest discomfort in order to diagnose AMI in elderly patients is decreased (Morrow, Antman, & Tanasijevic, 2001). It can be exemplified by diabetes mellitus which may not have chest pain during AMI (Ahmed, et al., 2013).

On the other hand, the numbers of participants over the age of 80 that have been recruited in the most elderly acute coronary syndrome trials are restricted; hence, limited resources are available for evidence-based management regarding this rapidly growing subset of ACS patients. Moreover, the presence of particular multiple chronic conditions and comorbidities in elderly patients may result in "atypical" or ‘’asymptomatic’’ presentations(Elbarouni, et al., 2009), it could preclude optimal evaluation of older adults with ACS.

AlthoughcTn has been well-known as the best biomarker to detect myocardial necrosis, there is little available data about cTn behaviors in elderly patients and even fewer in very old patients with AMI (Inbar, et al., 2009). Consequently, very old patients evaluated for excluding AMI are frequently prone to misdiagnosis (Borna, Frostred, & Ekelund, 2016).

Ithas been proven that that the lack of clinical standardization to determine the causes of cTn elevation in the elderly patients with AMI could lead to over diagnosis and misdiagnosis as well (Zhang, et al., 2016).

In the most recent clinical studies, despite including the geriatric patients in order to determine the relationship between cardiac troponin value and AMI, they are mostly grouped together in a single group without regrouping by age range, so the characteristics of cTn assays in AMI/ACS, particularly in very old patients with or without comorbidities have not been clarified precisely.

The influence of ageing and presence of comorbidities in diagnostic criteria for ACS or AMI is under question. Even though based on the 99th percentile of a healthy population, the cutoff value of hs-cTnT is less than 0.014 ng/mL (Noeller,et al,2003), its proper cutoff value in an elderly - particularly very elderly- population suffering from comorbidities with acute coronary syndrome is considered as a challenging diagnostic scenario. Few studies have suggested that the diagnostic value of the hs-cTnT levels might not be appropriate or might be different in elderly patients with comorbidities (Ferri, 2010; Zeller, et al, 2015; Mueller-Hennessen, et al., 2016).In contrast to these studies, some studies have suggested that cTn levels increase with age(Ferri, 2010; Reiter, Reichlin, Twerenbold, & Mueller, 2011; Anderson, 2011).

Therefore, an appropriate interpretation of an elevated hs-cTnT in elderly patients with comorbidities could have a considerable influence on ACS risk stratification.

Moreover, the hs-cTn assays have been shown to be associated with higher frequency of false-positive for AMI in very old patients (Ferri, 2010). It is reasonable to make an executive clinical decision in elderly patients with suspected acute coronary necrosis, age-based troponin values in the presence or absence of comorbidities should be considered.

In summary, the value of cTn in the elderly population is really not known and the present literature statement that it is increasing with age lead to its misuse and misinterpretation in the diagnosis of AMI.

Research question

In order to refine the risk stratification for AMI in elderly patients, particularly in very old patients, with or without comorbidities, the following questions have been raised:

- Could advancing age have an effect on the value of high-sensitive cardiac troponin T (hs-cTnT) in elderly patients with one or more comorbidity symptoms?
- Is there any relationship between cardiac troponin values with the advancing of age?
- What is the relationship between cardiac troponin values with comorbidities?

Literature review

An extensive search of original articles and reviews was done from 1990 to 2016. We used EMBASE and PubMed in addition to Scopus.

The key word “Acute coronary events”, with a combination of subtitles such as: [Acute myocardial infarction] OR [AMI] OR [ACS] OR [Myocardial Injury] OR [Myocardial Necrosis] AND [cardiac biomarkers] OR [Cardiac troponin] OR [cTn I] OR [cTn T] OR [Troponin assays] OR [hs-cTnT] OR [hs-cTnI] OR [99th percentile decision level for troponin] OR [Troponin assay impression] AND [aged people] OR [the population aged 65 years and older] OR [very old patients] OR [Older Adults] OR [In elderly Patients] OR [geriatric] OR [geriatric patients] OR [gerontology]

This research identified 231 publications that were analyzed first for the relevance of the title and abstract, and then reading the entire article. We only retained articles published in English or French between 1990 and August 2017, and reported data on AMI for a population aged 65 years and over. This study aimed to answer to questions referring to the relationship between age, comorbidities and acute coronary syndrome in aged patients, with respect to changes in the level of high-sensitive cardiac troponin T.

The literature review of the above-mentioned questions provided poor outcome, mainly due to inadequate consensus on the definition of elderly and very elderly in different studies. Consequently, the lack of studies on elderly patients, particularly very elderly confined our reviews ultimately to 20 articles.

The majority of these articles aimed to assess the diagnostic performance of high-sensitive cardiac troponin T in response to acute coronary events (Borna, 2016, Zhang and Hennessen 2015, Rains, 2014, Gore, 2013, Olivieri, Covino and Normann, 2012, Bahrmann, 2011, Reiter, 2010).

Although all mentioned studies utilized different methodology, their research produced the same results. Some studies revealed that having the elevated levels of hs-cTnT is a common finding in elderly patients without acute coronary heart diseases (Borna, 2016, Zhang, 2015, Reiter, 2010). In other words, they expressed doubts about the value of hs-cTnT in geriatric patients with suspected acute coronary events as it is already increased with advancing age. One study minimized the diagnostic role of hs-cTnT in very elderly patients (Covino, 2012).

Some researchers justified their result with possible influence of concomitant diseases on elevated troponin levels (Zhang, 2015, Normann, 2010). The main conclusions of the above studies were identical about the influence of age on troponin levels in elderly. In addition, the authors criticized the diagnostic characteristics of the troponin assays in the elderly. They proposed that an age-adjusted hs-cTnT cut-off value is necessary in elderly. One study concluded (Carro and Kaski, 2011), controversially that interpreting an elevated troponin in elderly as a myocardial necrosis may lead to over-diagnosis of acute myocardial infarction.

Other related studies in our literature review aimed to evaluate the prevalence of hs-cTn elevation in elderly and its association with comorbidities (Zeller and Webb, 2014, Eggers, 2008, Fromm, 2007, Myint, 2006 and Wallace, 2005). Although some of these studies have considered the association of increased hs-cTnI and concomitant diseases (Zeller, 2014 and Eggers, 2008), they have a common conclusion that is a positive association of elevated cardiac troponin in the presence of comorbidities among patients with acute cardiac coronary events. They concluded that the value of cardiac troponin depends on age, comorbidities, black race (Wallace, 2005), sex (Zeller, 2014) as well as acute coronary events.

The studies conducted by Reins and Myint (2014), and two other articles (Zaman, 2010 and Zethelius, 2005) aimed to investigate the prognostic role of elevated cardiac troponin and mortality. They found that the mortality rate was increased in elderly patients with acute coronary events and higher elevated troponin level.

In 2017, a study on impact of ageing on hs-cTnT in patients suspected of AMI (Taro Ichise et al, 2017) concluded that an accurate assessment of hs-cTnT in the elderly is necessary, particularly in presence of renal dysfunction.

Literature review conclusion

Despite the specificity of cardiac troponins (cTnT or cTnI) to detect acute coronary events, their applications in the elderly, particularly in very elderly patients, where the patient's medical history tend to be less reliable, require a proper interpretation in addition to consider the related clinical conditions that cause elevated troponin levels such as comorbidities. Furthermore, studies remain inconclusive to clarify whether elevated cardiac troponin levels are due to higher comorbidity, undiagnosed /silent ischemic heart disease, or an age-related phenomenon in elderly and very elderly patients. Moreover, the level of diagnostic value of cTn, among very old patients with or without comorbidities is still controversial.

Objectives

It is imperative to determine the predictive value of cardiac troponin in the elderly and very elderly patients to more accurately diagnose acute coronary events, particularly in those who have concomitant diseases.

The principal objective

The main objective of the present study is to determine the effect of age on the value of hs-cTnT in older adults with one or more comorbidities in order to predict the probability of occurrence of an acute coronary event. In other words, it is aimed to determine the level of hs-cTnT, which may change with different age and gender in elderly and very elderly patients, considering the presenceof comorbidities such as chronic heart failure, respiratory disease, renal or hepatic insufficiency, cancer and diabetes. Consequently, in addition to the significant variation in hs-cTnT that may influence mortality rate in the elderly patients, it should be taken into consideration according to the presence of or absence of concomitant diseases in order to manage the very old patients with ACS more accurately.

Hypotheses

Based on literature review, the role of hs-cTn in the detection of ACS/AMI in elderly patients has been investigated in a few research studies without a definitive conclusion. Moreover, there has been no extensive research to indicate the level of hs-cTnT in the very elderly patients with comorbidity. The lack of in depth study of the above issue is the motive of this study.

We suppose that due to pathophysiological changes in the very elderly who have no clinical signs of cardiac necrosis, there is an age-related increase of serum troponin levels. Consequently, it is hypothesized that hs-cTn should be adapted for different age groups in very elderly patients with the presence or absence of comorbidities in order to improve the diagnostic accuracy of acute coronary events in geriatric patients.

It also could be hypothesized that the level of hs-cTnT increases with the presence of one or more comorbidities.

Methodology

Two local hospitals of Sherbrooke University, CHUS - Fleurimont and CHUS - Hôtel-Dieu have participated in this retrospective observational cohort study. The medical record data of participants in the present study have been evaluated from 2012 to 2016.

Targeted population

Participants of the study were all patients, aged 65 years and over, admitted at the CHUS - Fleurimont and Hôtel-Dieu sites for suspected ACS between the period from January 2012 to December 2016 in and for whom serial analysis of hs-cTnT levels have been performed . In all, 6,977 elderly patient records have been identified.

Exclusion criteria

- ➢ The subjects with myocardial infarction over previous 365 days.
- ➢ Postoperative AMI
- ➢ Missing data in medical record
- ➢ All geriatric patients who experienced cardiac arrest

Variables

Two types of variables were included in present study:

1. <u>The main variable(dependent)</u>:
    - ➢ Hs-cTnT values
    - ➢ List of comorbidities: diabetes, chronic heart failure, coronary artery disease, respiratory disease (e.g. COPD), renal or hepatic insufficiency, cancers, hypertension, neurocognitive disorders, hypothyroidism, anemia, cardiomyopathy, pulmonary hypertension, pulmonary embolism, pneumonia, stroke, atherosclerotic vascular disease, subarachnoid hemorrhage, cardiovascular disease

2. demographic variables(independent): age and sex

Ethical considerations

This is a retrospective cohort medical records study that the data was collected previously. Therefore, there is no recruitment process. The research ethic committee of CIUSSS de l'Estrie-CHUS. Access of patient records was allowedonly as fully anonymized medical records. In other words, there is no access to nominal information, so it is impossible to identify participants. In addition, to ensure the confidentiality, the obtained data were stored in a new file and in order to enhance the security of data, the created file was encrypted in researcher's computer. Furthermore, the results of the present study will be published in aggregate and anonymous form. No serious risks were provided by the present study, for the participants (here the anonymous medical records) or the society, according to the nature of this study.

Statistical approach

Continuous variables were expressed as means +/- standard deviation (SD).Categorical variables were expressed as absolute values and percentages of the total.Independent t-Tests (to compare the troponin value between different age groups). Chi-square tests or Pearson $\chi 2$ tests (to evaluate the difference in the prevalence of comorbidities according to the level of troponin). Multivariate logistic regression (to quantify the risk of having a high level of troponin associated with age and comorbidities). Data were analyzed using SPSS (v24; IBM, USA). The statistical significance level of study was set at a $P < 0.05$.

Anticipated result

It is predicted:

- ➢ To confirm a significant differences of hs-cTnT values by sex and age groups
- ➢ To determine an elevated of hs-cTnT with confirmed comorbidity

Data sources: We used the administrative database (InfoCentre) that records patients admitted to the CIUSSS- Estrie CHUS and includes all elderly patients, to identify patients with comorbidities and at least one hs-cTnT level analyzed data.We reviewed the records of all patients to evaluate demographic and clinical characteristics as age, sex, and pre- existing comorbidities.

Outcomes: A total of 6977 medical records of patients aged ≥ 65 years were included in the study data base. After excluding all medical records with the previous or post-operative AMI and any experienced cardiac arrest, medical records of 6822 elderly patients were grouped into three age groups: patients aged 65 to 74 years (young-old), patients aged 75 to 84 years(old) and patients ≥85 years old(old-old).

Biomarker assay: Patients were presented in this study had serial measurement of hs-cTnT. The first blood sample for of hs-cTnT measurement that was collected at time of admission to the hospital or emergency department was considered. In our hospitals, hs-cTnT is measured using the elecrochemiluminescence immunoassays with Roche Elecsys analyzers (Troponin T Stat, Roche Diagnostics, F. Hoffmann-La Roche Ltd, Basel, Switzerland), with a limit of detection of 3 ng/L.

Results:

Three thousand four hundred and thirty-nine male patients (50, 4%) and three thousand three hundred and eighty-three female patients (49. 6%) were included in this study. Table I shows demographic and clinical characteristics of the study cohorts. Seventeen significant comorbidities were identified in our sample and consist of anemia, Cerebrovascular accident(CVA), malignancy, cardiomyopathy, coronaropathy, pulmonary embolism(PE), subarachnoid hemorrhage(SAH), diabetes, Arterial hypertension(AHTN), pulmonary hypertension(PHTN), hypothyroidism, renal insufficiency(RI), atherosclerosis vascular disease(AVSD), chronic obstructive pulmonary disease(COPD), obesity, pneumonia, and neurocognitive disorder(NCD). The maximum age of 104 was found in this study that included one man and one women. The aged man was suffering from four comorbidities (anemia, SAH, HTN and pneumonia) with hs- cTnT value of 42 ng/l , while the aged women was suffering from seven comorbidities (CVA , HTN , RI , NCD, hypothyroidism, coronaropathy, and pneumonia) with hs-cTnT values of 30 ng/l. We also identified that the arterial hypertension was the most frequent comorbidity while the cardiomyopathy that was the least frequent condition in our sample.

Table I. Demographic and clinical characteristics of the study cohort

The variables	65-74 years old (n = 2555)	75-84 years old (n = 2490)	≥85 years old (n =1777)	All patients (N = 6822)
Age($\bar{x}$ ± SD)	**69 ± 2.83**	**79 ± 2.88**	**89 ± 3.62**	**78.3 ± 8.3**
Sex (N. %)				
Men	**1469. 57**	**1294.52**	**649.36**	**3439.50.4**
Women	**1059.43**	**1196.48**	**1128.64**	**3383.49.6**
Hs-cTnT ng/l ($\bar{x}$ ±SD)	**93±312.15**	**77±234.46**	**63±162.73**	**79±252.14**
Men	**104±353.0**	**80±183.73**	**70±125.32**	**89±264.64**
Women	**78±242.34**	**74±279.19**	**59±180.71**	**70±238.45**
Comorbidities (%. N)				
Quartile I (19.4. 1291)				
Men	**283. 48**	**228.52**	**132.61**	**643.48**
Women	**349.52**	**207.48**	**83.49**	**684.52**
Quartile II (15.4. 1048)				
Men	**169.39**	**188.48**	**149.58**	**506.48**
Women	**263.61**	**204.52**	**78.42**	**545.52**
Quartile III (19.8. 2030)				
Men	**313. 41**	**355.48**	**354.67**	**1022.51**
Women	**442.59**	**392.52**	**174.33**	**1008.49**
Quartile IV (35.4. 2414)				
Men	**294.43**	**425.46**	**493.61**	**1212.51**
Women	**397.56**	**491.54**	**314.39**	**1202.49**

Hs-cTnT (High-sensitivity cardiac Troponin T), ng/l= nanogram/liter, Quartiles (I=1-2 comorbidities, II=3 comorbidities, III=4-5 comorbidities, IV= ≥ 6 comorbidities)
Patients were divided into 3 categories according to the tertile of hs-cTnT concentration with tertile 1 (0-14 ng/L = low level: normal, according to the manufacturer instructions), tertile 2 (15-31 ng/L=moderate level) and tertile 3 (≥32 ng/L=high level). Furthermore, patients were grouped into four categories according to the presence of comorbidity with: quartile 1 (one or two comorbidity), quartile 2 (three comorbidities), quartile 3 (four to five comorbidities) and quartile 4 (≥ 6 comorbidities).

Two thousand four hundred and fourteen patients had six or more comorbidities (35. 4%).The average age and hs-cTnT level of our sample was 78.3 years, and 79.9 ng/L respectively. Table II shows general characteristics of the study cohorts according to the defined variables. The standard deviation of total and all quartile from the mean of troponin level was considered significant.

Table II. General distribution of hs-cTnT of the study cohorts, according to sex.

The variables	**Total ($\bar{X}$ ± SD)**	**Men ($\bar{X}$ ±SD)**	**Women ($\bar{X}$ ±SD)**	**P-value**
HS-cTnT, ng/l ($\bar{X}$ ±SD)				
Q I	79 ± 324.68	93± 416.20	65 ± 181.78	p>0.05
Q II	81 ± 290.86	89±263.39	71±317,80	p>0.05
Q III	89±264,02	97±242,62	81±283,43	p>0.05
Q IV	71±161,85	66±203,50	76±119,84	p>0.05

Quartiles (I=1-2 comorbidities, II=3 comorbidities, III=4-5 comorbidities, IV= ≥ 6 comorbidities), Hs-cTnT (High-sensitivity cardiac Troponin T), SD (standard deviation)

In both sexes, the troponin value across all age groups, with any types of comorbid disease, was remarkably high (> 32 ng/l). In men, the hs-cTnT value was decreased for both old group and old-old group compared to the young-old group, that was statistically significant ($p < 0.05$) .

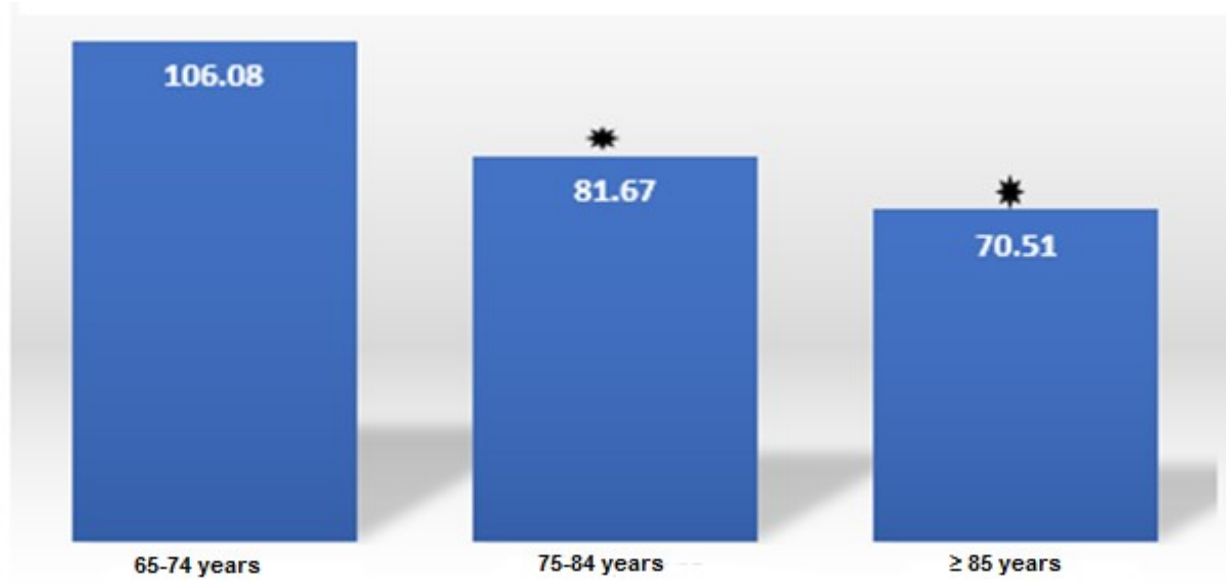

Figure 25.High-sensitive cardiac troponin T level in all male age groups (* means statistically significant, p<0.05)

Although the hs-cTnT values in women had shown to have decreased, the difference was statistically not significant in all age groups.

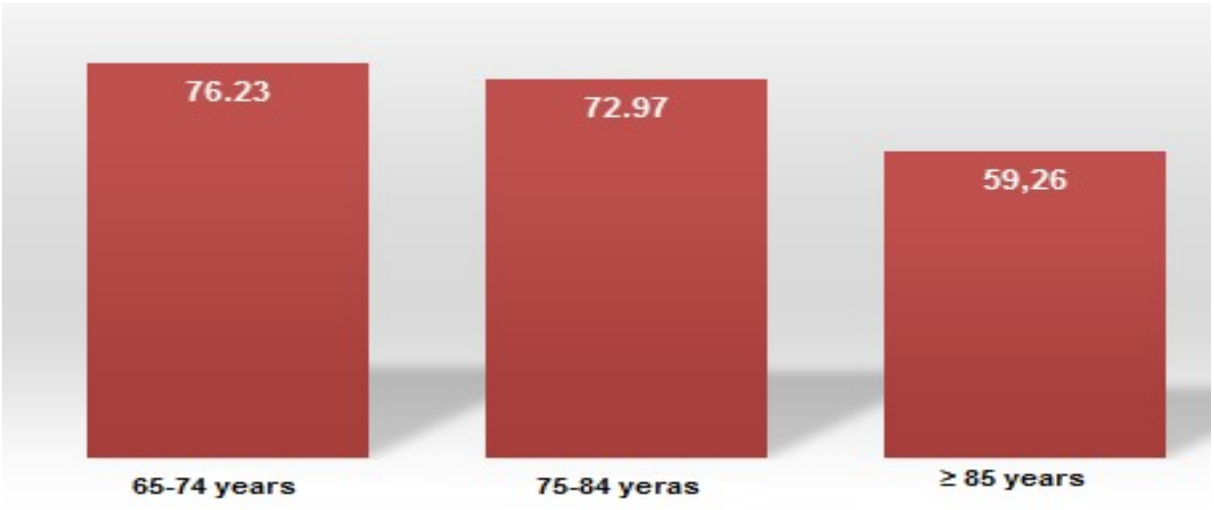

Figure 26.High-sensitive cardiac troponin T level in all female age groups

The distribution of hs-cTnT with regards to age and comorbidities is shown in table III. Obviously, the troponin level was decreasing according to age for each comorbidity, although not statistically significant.

Table III. General distribution of hs-cTnT of the study cohorts, according to age and comorbidity.

The quantiles	**65-74 years old (X̄ ±SD)**	**75-84 years old (X̄±SD)**	**≥85 years old (X̄±SD)**	**P-value**
I (1-2 comorbidities)	93 ± 423.99	70 ± 190.18	53 ± 102.50	p>0.05
II (3 comorbidities)	92±272,50	80±368,09	59±127,67	p>0.05
III (4-5 comorbidities)	103±314.94	91±266,42	67±158,85	p>0.05
IV (≥ 6 comorbidities)	82 ± 171.87	67±127,75	64±185,59	p>0.05

Furthermore, the presence of hypertension and renal insufficiency made an exception that it was statistically significant as shown: The hs-cTnT level decreased in the presence of arterial hypertension in both groups of old and old-old, whereas, the troponin level decreased only in group of old-old in the presence of renal insufficiency ($p<0.05$) (Fig.14). The highest troponin levels were discovered in patients with renal insufficiency; in contrast, the lowest troponin levels belonged to patients with neurocognitive disorders.

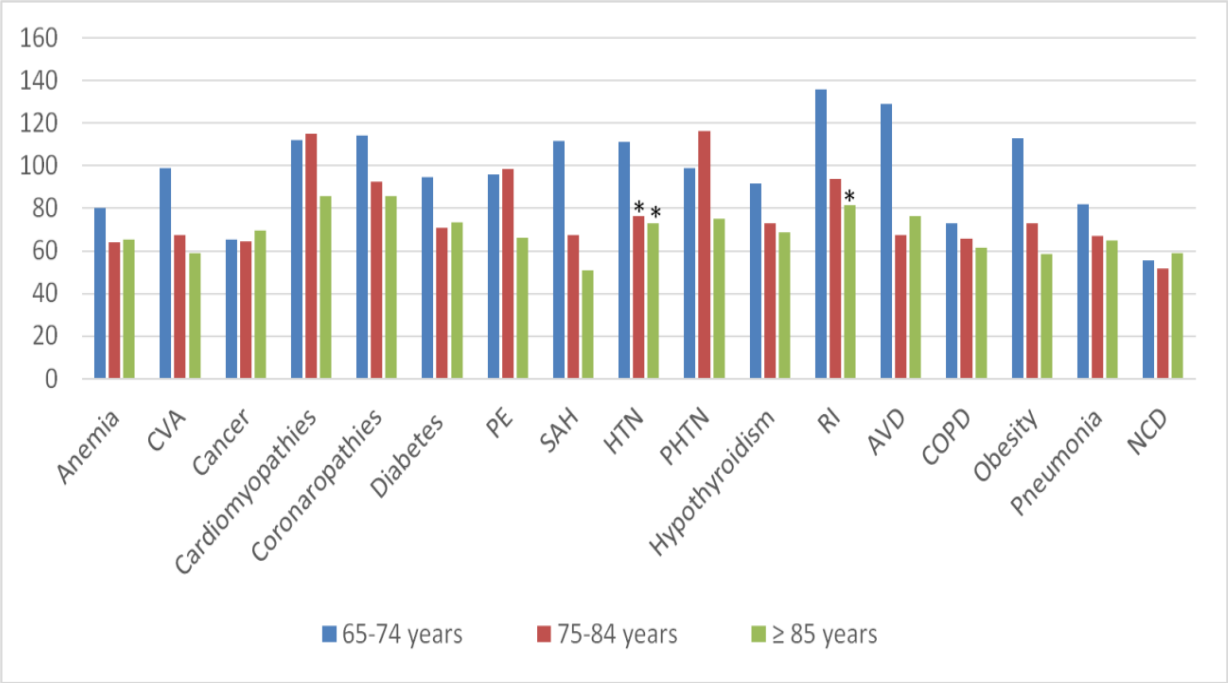

Figure 27.Troponin value of age groups in men with different commodities. CVA= cerebrovascular accident, PE=pulmonary embolism, SAH= subarachnoid hemorrhage, HTN=hypertension, PHTN = pulmonary hypertension, RI=renal insufficiency, AVD= atherosclerotic vascular disease, COPD=chronic obstructive pulmonary disease, AND=neurocognitive disorder. * Statistically significant, Chi-square tests used to compare between troponin levels and age sub-groups and comorbidities.

Noticeably, in women the highest troponin levels were discovered in patients with cardiomyopathy, that were strongly elevated, in contrast, the lowest troponin levels were detected in patients with neurocognitive disorders.

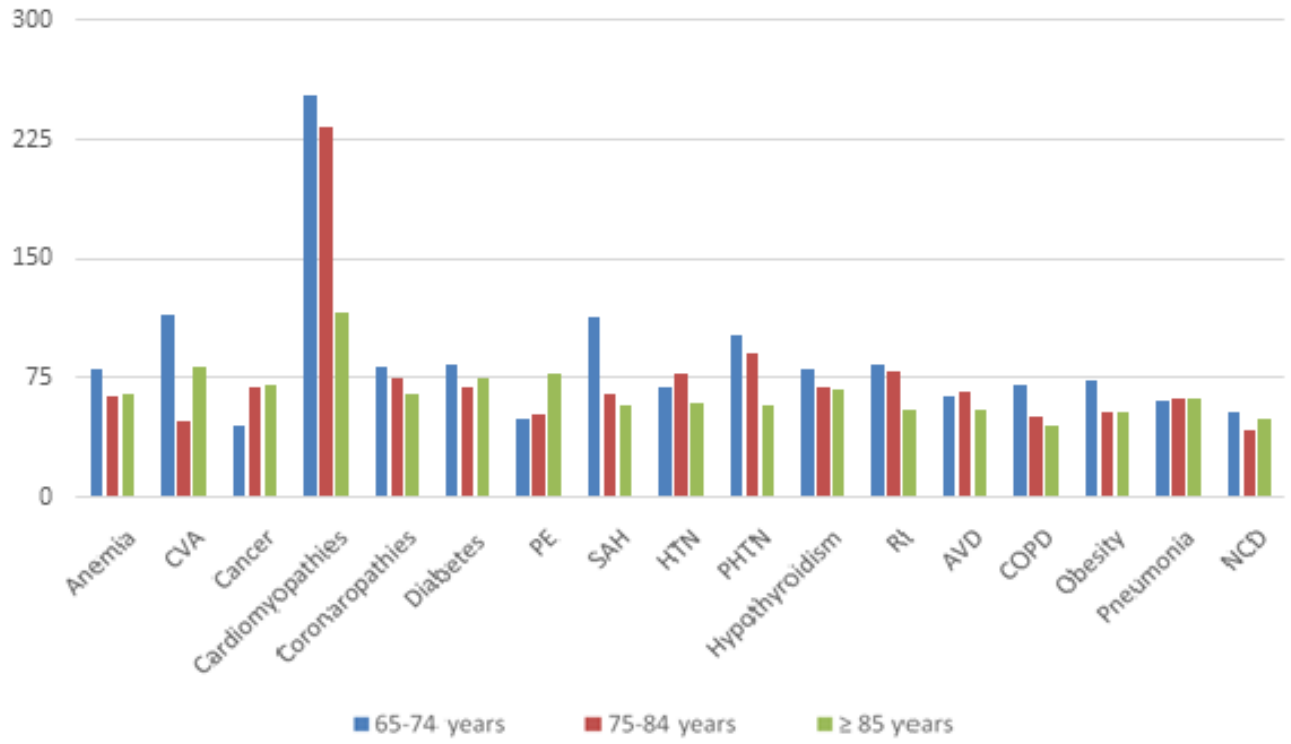

Fig 28. Troponin value of age groups in women with different commodities.
CVA= cerebrovascular accident, PE=pulmonary embolism, SAH= subarachnoid hemorrhage, HTN=hypertension, PHTN = pulmonary hypertension, RI=renal insufficiency, AVD= atherosclerotic vascular disease, COPD=chronic obstructive pulmonary disease, AND=neurocognitive disorder. Chi-square tests used to compare between troponin levels and age sub-groups and comorbidities.

Clearly, the troponin levels were decreased as a function of age among all comorbid conditions ($p > 0.05$). In fact, among all pre-existing medical conditions, the highest levels of troponin were observed in the young-old group (65 to 74 years old). Cancer and pulmonary embolism, were two exceptions, whereas, troponin values were more elevated in both old groups. Indeed, the young old-group (65-74 years old), among all comorbidities, were most affected by elevated troponin levels, except for two comorbidities: cardiomyopathy and pulmonary hypertension, where troponin values were more elevated in old group (patients aged ≥ 75 and 84 years). After calculating the average amount of hs-cTnT levels for each age group, it was discovered that the patients in the younger cohorts had higher elevated rates of hs-cTnT values. In men, troponin values across all quartiles of comorbidities were decreased as a function of age (Fig. 16). In other words, the highest values of troponin were detected in young-old group, whereas, the lowest values were shown in old-old group.

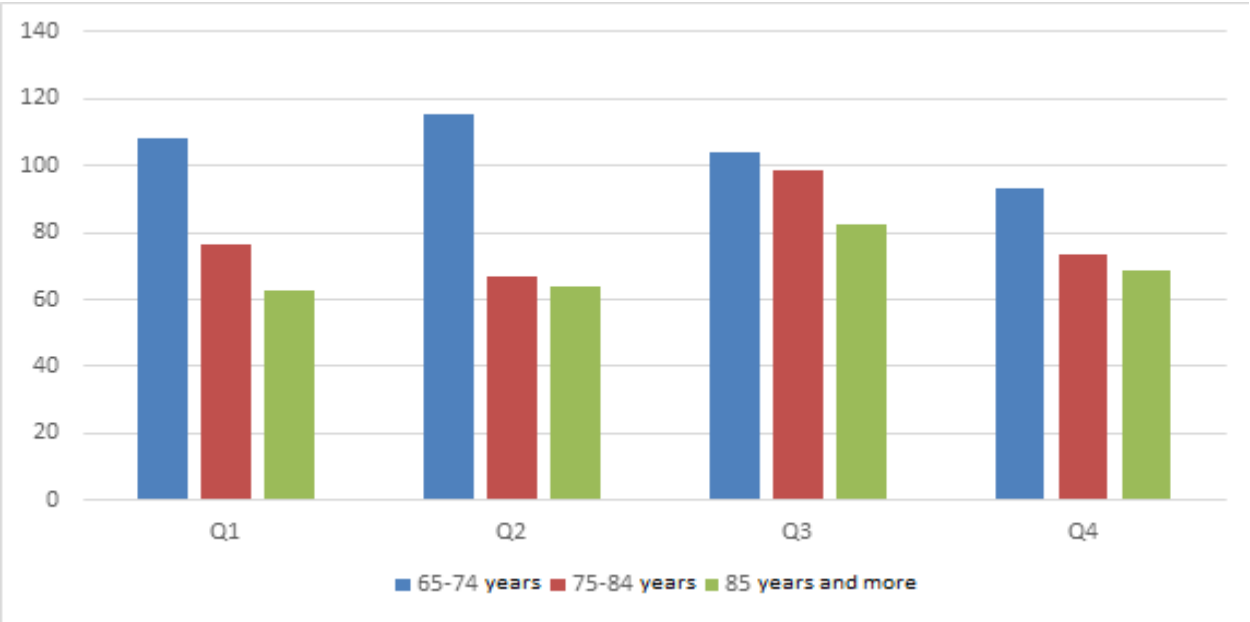

Fig 29. Troponin value of age groups in men with different comorbidities. Quartiles (I=1-2 comorbidities, II=3 comorbidities, III=4-5 comorbidities, IV= ≥ 6 comorbidities).

Although in women, troponin values across all quartile of comorbidities were decreased with advancing age (p>0.05), (Fig.17), in the second quartile group (Quartile II), the highest troponin levels were shown in old group (patients aged 75-84 years).

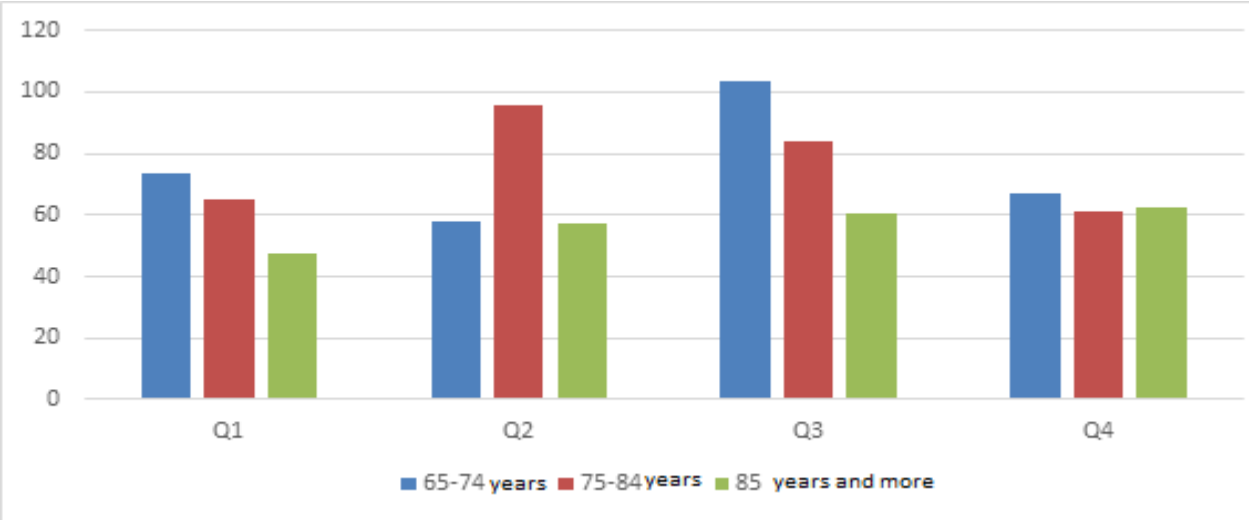

Fig 30. Troponin value of age groups in women with different comorbidities. Quartiles (I=1-2 comorbidities, II=3 comorbidities, III=4-5 comorbidities, IV= ≥ 6 comorbidities).

Although in both sexes hs-cTnT values were decreased with advancing age in all quartiles, it did not come out statistically significant ($p>0.05$).

Odd Ratio

Obviously, the probability of having raised levels of troponin was increased with all types of comorbidities. But contrary to our first data analysis as explained above, when we applied odds ratios instead, the Hs-cTnT levels increased with advancing age.In order to found the reason for observed inconsistency, a further analysis of data was conducted.

In our pooled analysis of patients' medical records, plasma levels of Hs-cTnT had a non-parametric distribution. In other words, the level of Hs-cTnT was extremely the level above the reference range, that means a lot of patients had raised Hs-cTnT level more than 33 ng/l whereas the standard deviation that was of greater magnitude than its mean.

Therefore, we applied the median to present Hs-cTnTvalues (interquartile range).

Table IV-the median distribution of Hs-cTnT of the study cohorts, according to age and comorbidity

	Male	**Female**
	Median [Q1 ; Q3]	Median [Q1 ; Q3]
65-74 years	24,0 [13.0; 57.2]	19,0 [9.0 ; 45,2]
75-84 years	33,0 [19.0; 63,0]	24,0 [14.0 ; 48,0]
85+ years	39,0 [25.0; 67,2]	31,0 [20.0 ; 52,0]

Q1: 25 percentile; Q3: 75 percentiles

Apart from the mean, even after the application of the median, it was shown that the Hs-cTnT levels increased in the presence of comorbidity in both groups of men (Figure 29) and women (Figure 30).

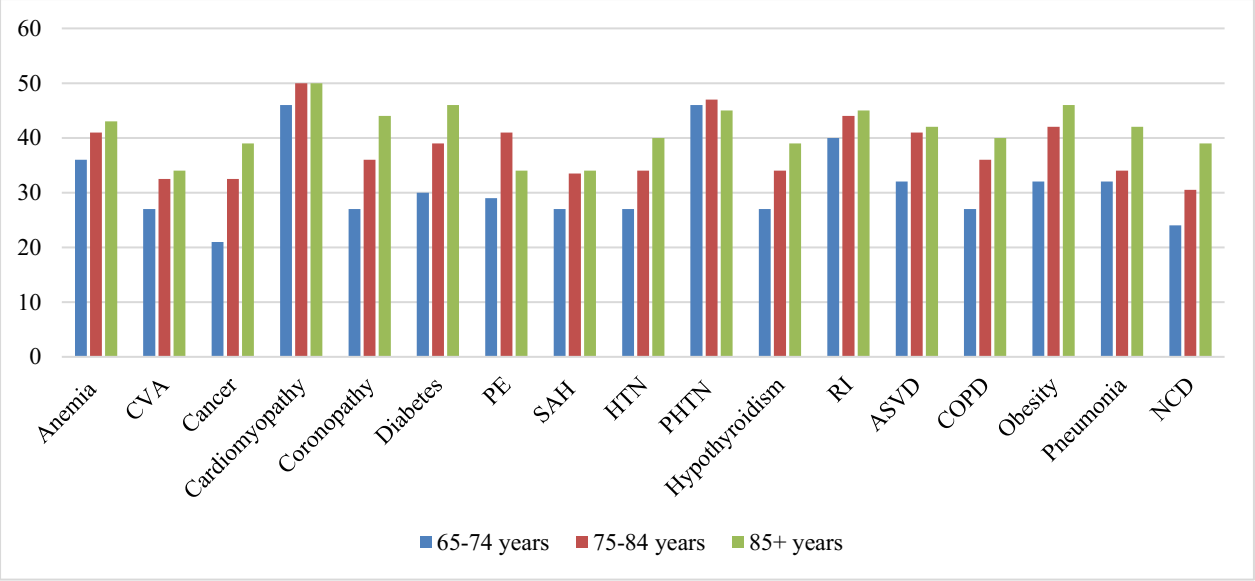

Figure 31. Troponin value of age groups in men with different commodities. CVA= cerebrovascular accident, PE=pulmonary embolism, SAH= subarachnoid hemorrhage, HTN=hypertension, PHTN = pulmonary hypertension, RI=renal insufficiency, AVSD= atherosclerotic vascular disease, COPD=chronic obstructive pulmonary disease, AND=neurocognitive disorder.

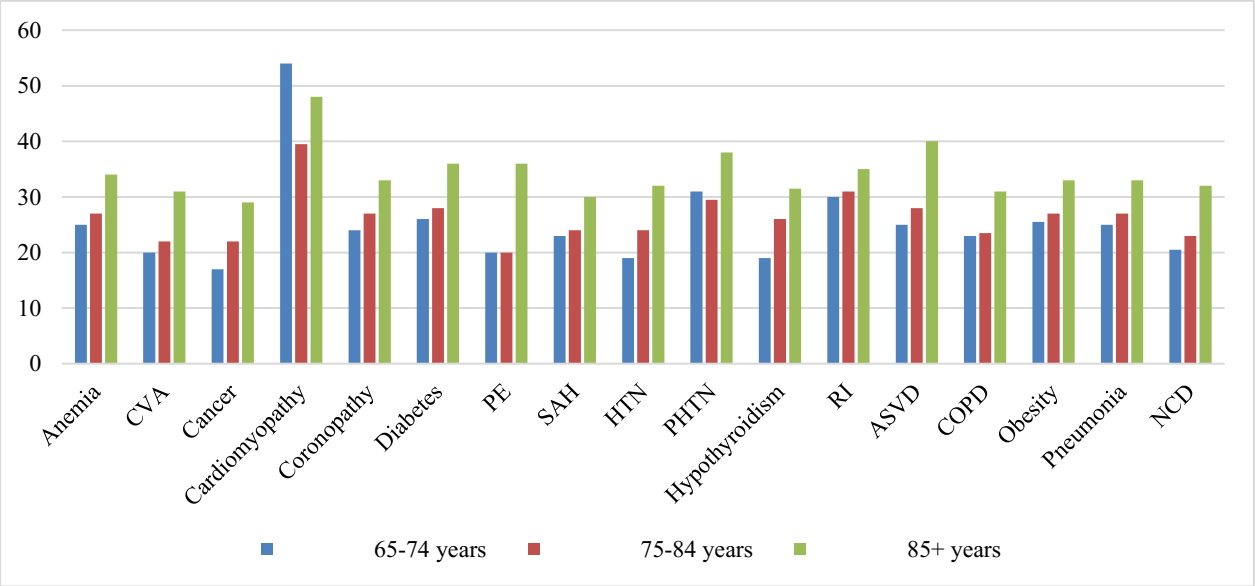

Figure 32. Troponin value of age groups in women with different commodities.CVA= cerebrovascular accident, PE=pulmonary embolism, SAH= subarachnoid hemorrhage, HTN=hypertension, PHTN = pulmonary hypertension, RI=renal insufficiency, AVSD= atherosclerotic vascular disease, COPD=chronic obstructive pulmonary disease, AND=neurocognitive disorder.

The measure of effect, here age, is expressed as odds ratio which is not influenced by troponin levels.

Apparently, with each increase in the number of comorbidity in men's group, the risk of having a moderate and high level of hs-cTnT has shown to have increased by 1.38 [1.3; 1.44] and 1.22 [1.16; 1.28].In groups of men, the odd ratio of high dose and moderate dose of troponin was discovered highest in old-old and old group respectively. In other words, the odds ratio for elevated troponin level and age was more than 1 in both women and men. In fact, within each of the troponin tertiles, index levels on age quartiles were significantly increased with the increase of age, and vice versa.

Table V. Odd Ratio in men, by considering age groups and comorbidities

Male						
Reference category: Hs-cTnT (0-14ng/l) = Low level N = 666	Hs-cTnT (15-31ng/l) =moderate level N=1125			Hs-cTnT (≥32ng/l) =high level N=1648		
	OR	95% CI	P value	OR	95% CI	P value
Sum of the comorbidities	1.22	[1.16 ; 1.28]	p<0.001	1.38	[1.31 ; 1.44]	<0.001
Old group [75-84 years old]	2.03	[1.63; 2.52]	p<0.001	2.13	[1.73; 2.63]	<0.001
Old-old group [≥ 85 years old]	4.49	[3.10; 6.50]	p<0.001	5.61	[3.92; 8.03]	<0.001
Young-old group [65-74 years old]	1			1		

Reference group: 1, CI= confidence interval. Multivariate logistic regressions were performed to quantify the risk of having a high level of troponin according to age and comorbidities.

More clearly, the odds ratios of 2.13 means that a patient aged between 65 and 74 years has 2.13 times "risk" of being in the high level group compared to the moderate level group (2.03 times) which might be interpreted as the hs-cTnT value almost increases more with advancing age (p<0.001).

The same conclusion can be drawn with regard to the difference in odds ratios of 4.49 and 5.61 means that a patient aged 85 years and more has a 4.49 times risk of being in the moderate level group compared to be in the high level troponin group (5.61) which could present the increased probability of having increased troponin level in old-old group (p<0.001).

In women groups, like men groups, the odd ratio of the maximum increased troponin levels was shown in old-old group and old group respectively.

Table VI. Odd Ratio in women, by considering age groups and comorbidities

Female						
Reference category: Troponin (0-14ng/l) = Low level N = 860	Hs-cTnT (15-31ng/l) =moderate level N=1176			Hs-cTnT (≥32ng/l) =high level N=1347		
	OR	95% CI	P value	OR	95% CI	P value
Sum of the comorbidities	1.23	[1.18 ; 1.28]	p<0.001	1.26	[1.21 ;1.32]	<0.001
Old group [75-84 years old]	1.53	[1.25 ; 1.89]	p<0.001	1.70	[1.37; 2.10]	<0.001
Old-old group [≥ 85 years old]	4.45	[3.47 ; 5.70]	p<0.001	4.55	[3.53; 5.82]	<0.001
Young-old group [65-74 years old]	1			1		

Reference group: 1, CI= confidence interval. Multivariate logistic regressions were performed to quantify the risk of having a high level of troponin according to age and comorbidities.

Similarly, in women group, the odds ratios of 1.70 means that a patient aged between 65 and 74 years has 1.70 times “risk” of being in the high level group compared to the moderate level group (1.53 times) which might be interpreted as the hs-cTnT value almost increases more with advancing age (p<0.001).

The same conclusion can be drawn with regard to the difference in odds ratios of 4.45 and 4.55 means that a patient aged 85 years and more has a 4.45 times risk of being in the moderate level group compared to be in the high level troponin group (5.55) which could present the increased probability of having increased troponin level in old-old group (p<0.001).

Definitely, with each increase in the number of comorbidity in women's group ,the risk of having a moderate and high level of Hs-cTnT has shown to have increased by 1.23 [1.18; 1.28] and 1.26 [1.21; 1.32].

In order to evaluate the effect of age and comorbidity burden on serum concentration of Hs-cTnT, adjusted OR was included to our logistic regression model.

Table VII- Adjusted Odds Ratio for one comorbidity and for a year of ageing

	Tertile of hs-cTnT	**AOR**	**95% CI**	**P value**
2	Burden of disease	1.216	[1.178, 1.255]	p<0.001
	Age	1.070	[1.061,1.080]	p<0.001
3	Burden of disease	1.311	[1.272, 1.352]	p<0.001
	Age	1.073	[1.064, 1.082]	p<0.001

Reference category is: 1, CI= confidence interval. AOR= Adjusted Odds Ratio

Apparently, advancing age and having comorbidity could increase the hs-cTnT levels, that means advancing age or presence of comorbidity elevate the chance of being in moderate troponin group(2) or high troponin group(3),compare to the low troponin group(1), p<0é001).

Surprisingly, with regards to the table of adjusted OR (Table VII), if we consider a year of aging and one comorbidity in continuous, so the OR of having raised troponin shows more influenced by having comorbidity, compare to ageing (adjusted OR for burden of disease 1.216 compare to age that is 1.070 in group 2, and adjusted OR for burden of disease 1.311 compare to age that is 1.073 in group 3), (p<0.001).

Statistical Conclusion

Given above results, it is confusing that the figures25, 26, 29, and 30 show the level of troponin increases with advancing age, while the results from odds ratio, in the contrary show that patients aged 75 to 84 and 85 years and older were significantly more likely to have a moderate and high level of troponin than low compared to individuals aged 65 to 74 years.

In other words, our sub-analysis demonstrated that in both sexes, the patients aged between 65 and 74 years the mean ($\bar{x}$) of Hs-cTnT values (the difference between the largest and the smallest values, [min; max]) is much bigger than the 75-84 age group and 85 and over.

To make it clearer, similarly among women and men aged 65 to 74 aged, the extreme values of Hs-cTnT were found. It can be exemplified by an individual with an Hs-cTnT value of 9258 ng/l (which would probably be clinically correct) which could influence the Mean ($\bar{x}$).

The main disadvantage of the Mean ($\bar{x}$) in statistical analysis refers to its susceptibility to the impact of outliners, so the Mean cannot be representative of the values in the sample. Therefore, in this situation, it would be preferred to have a more accurate measure of central tendency. In this case, from a statistical point of view, the use of the Median [Q1: 25 percentile; Q3: 75 percentiles] which is not influenced by extreme values, seems more precisely.

By applying the median, it could be shown that the Hs-cTnT values increases with advancing age in both men and women (Table VI).The odds ratio was used to determine whether advancing age is a risk factor for an elevated cardiac troponin level, and to compare the magnitude of advancing age or effect of comorbidities for that outcome.

As a brief reminder (Raydurg, et al.2016):

OR/AOR=1 Exposure does not affect odds of outcome

OR/AOR>1 Exposure associated with higher odds of outcome

OR/AOR<1 Exposure associated with lower odds of outcome

While interestingly, by driving AOR, the probability of having an elevated Hs-cTnT will relate to the presence of comorbidities, not advancing age (Table VII). In other words, ageing could not be a risk factor to increase cardiac troponin levels in elderly.

It could be concluded that among elderly patients, in both sexes, with abnormal cTnT values, older patients were more likely to have an elevated troponin level compared to the younger cohorts due to the presence of comorbidities, but not ageing ($p<0.001$).

Discussion:

Although the hs-cTnT is a marker that has made a significant contribution to the diagnosis of myocardial acute events, the interpretation of abnormal hs-cTnT levels remain as a debate amongst geriatric cardiologists. It could become a challenging issue facing the elderly patients with vague ischemic symptoms, atypical ECG and abnormal cTnT levels, since that is proven that certain adverse outcome in acute coronary events increase with age (Ngako, et al, 2009).

This study aimed to determine the influence of age on the value of hs-cTnT in older adults with one or more comorbidities to improve prediction of acute coronary events in elderly.

The results of the present study, in elderly and very elderly patients suffering from different comorbidities, show that the presence of comorbidities compared with advancing age has more affect on hs-cTnT level. In contrast, the troponin rises in the absence of AMI or ACS resulted from the presence of comorbidities

The main significant novelty of present study is to exclude acute cardiac events in order to eliminate the role of cardiac injury on increasing hs-cTnT levels, and to consider the comorbidities in sample pools as well. That means that the effects of advancing age and acute coronary events, as a confounding bias, are diminished.

In our literature review, among the present comorbidities that have included in different studies, almost all papers indicated that the renal dysfunction and congestive heart failure are the reason of increased hs-cTnT values in geriatric patients (Mahajan, et al,2006;Lamb, Webb, & Abbas, 2004 ;Freda, et al.,2002).

In almost all previous similar studies where the individuals were screened to rule out ACS, the majority of these studies have justified the increased hs-cTnT level as related to the advanced age if the acute cardiac events could be excluded.Although in these studies the comorbidities were presented, the authors only indicated that the reason for increased hs-cTnT was levels related to advanced age(Missov., & De Marco, 1999;Ferri, 2010; Reiter, Reichlin, Twerenbold, & Mueller, 2011;Zaman, et al.,2011;Carro, & Kaski,2011;Anderson, 2011;Covino, et al.,2012; Olivieri, et al.,2012;Rains, Laney, Bailey, & Campbell, 2014;Gore, et al.,2014;Zeller, et al.,2015;Webb, et al., 2015).In other words, the age has been considered as a risk factor for elevated hs-cTnT,which means the hs-cTnT level is elevated by advancing age *per se*.

Although only a few studies have suggested the influence of comorbidities on raised hs-cTnT, they were more attributed to the effect of advancing age (Zethelius, Johnston, & Venge, 2006; Gravning, et al, 2014). Several studies have considered the influence of ageing on hs-cTnT is significant, consequently they have underestimated the diagnostic role of hs-cTnT assay in acute coronary event profiles (Lamb, Webb, & Abbas, 2004; Mahajan, et al., 2006). While, our data analysis could suggest a different interpretation of rising hs-cTnT levels in elderly, namely the hs-cTnT could still be a sensitive and very useful acute cardiac biomarker to detect acute coronary events, and could play a more significant role in ACS diagnosis in aged patients, mainly old-old patients if other reasons of its elevation are taken into consideration such as other causes (co-morbidities) of increased hs-cTnT levels.

A study of factors affecting hs-cTnT values has shown that the hs-cTnT levels are higher in men and increases with age in both men and women (Noeller, et al., 2003).Our results fit with the first part of mentioned study, which means that the basic levels of hs-cTnT is increased in men compared to women, but controversially our evidences have shown that the hs-cTnT levels are not changed with age in both sexes.

As the previous studies have significantly interpreted the elevated of hs-cTn values as an effect of advancing age (Missov., & De Marco, 1999; Ferri, 2010; Reiter, Reichlin, Twerenbold, & Mueller, 2011; Anderson, 2011; Olivieri, et al., 2012), our data analysis shows that the possible causes of the increased hs-cTnT in elderly population are due to the presence of different comorbidities, not only advancing age. While the elevated hs-cTnT values are considered as result of advancing age, it may be concluded that the hs-cTnT assay is not a reliable criterion to exclude or include acute cardiac events in diagnosis of geriatric patients. On the contrary, at the absence of a thrombotic complication of coronary artery disease in elderly patients, an elevated hs-cTnT value could be interpreted as a marker of undiagnosed concomitant disease, the “false positive rate” declines substantially.

To our knowledge, this study is the first to document that advancing age has a less to play a role in elderly patients with high hs-cTnT concentrations. Based on the results of present study, the elevated levels of hs-cTnT in aged patients without any acute cardiac events is further due to other causes and less frequently from advancing age.

Conclusion

It is shown that there is an overall increase of Hs-cTnT values in all groups of comorbidities. Our findings suggest that in elderly patients the association of elevated Hs-cTnT and advanced age is under question, so regardless of the presence of comorbidity, increased Hs- cTnT value should be taken into account for the diagnosis of ACS and should not divert attention from other underlying clinical problems. It is suggested that patients' comorbidity should be taken into consideration when ruling out acute coronary events and/or adverse prognostic implications in patients who have very high hs-TnT concentrations. In other words, advanced age could not be associated to an elevation of Hs-cTnT; in contrast, cardiac troponin elevation is the result of pre-existed comorbidities independently of their number. Increased troponin level in elderly should always be considered as pathological and a specific etiology searched.

Study strengths

In the current study, our sample size was extremely large, so in our statistical analysis the t-test has so much power that even a miniscule difference was flagged as statistically significant. On the other hand, we recruited the medical records of a large heterogeneous elderly populations, who were divided into three main aged group with seventeen comorbidities, so our results could be applied or generated to represent group of elderly patients, as a whole. This research study was unique, that can be concluded advancing age should not be considered as the only risk factor for raised hs-cTnT.

Study Limitations

In our study, the evaluation of hs-cTnT accuracy was limited since the data was collected only on elderly patients with different comorbidities, without having much awareness of their concomitant therapy. In other words, it is not possible to justify the presence of different comorbidity, how much it could increase the level of hs-cTnT values. Therefore, we cannot speculate the variance of the hs-cTnT values in elderly patients who were affected by different concomitant diseases with respect to their comorbidity.

The other limitation of the current study is the lack of information about the patient's medications and their medical history in our data base.

Lastly, in this study, although the data was included from a large cohort of patients, these data are observational, so further interventional studies are needed to detect the impact of each comorbidity with considering age and sex.

Future directions

Features of acute coronary events in elderly and very elderly patients comprise life-threatening conditions that require immediate and efficient medical intervention to improve prospective outcomes, particularly at the presence of atypical singes and symptoms. Judicious interpretation of increased hs-cTnT levels is particularly essential in different fields of medicine particularly in emergency wards, intensive care units and geriatric cardiology. Clinical assessment with use of para-clinical data is critical for an accurate and prompt diagnosis followed by appropriate management. Thoughtful interpretation of hs-cTnT levels may yield insight into physio-pathological mechanism of the concomitant condition that causes the raised hs-cTnT in elderly. Furthermore, future directions should aim to find the cut-off level for hs-cTnT levels at the presence of different comorbidities in acute coronary events, and study the relationship between mortality and increased levels of troponin in elderly patients with different comorbidities as well.

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Increased level of high-sensitivity cardiac Troponin T in a geriatric population is determined by comorbidities compared to age

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ABSTRACT

High level of cardiac Troponin T (hs-cTnT) in geriatric population has been considered as an age-related phenomenon, which may question the interpretation of the increase of hs-cTnT in this population. The challenge is what is the primary cause of the increased hs-cTnT levels in elderly patients without AMI.

Objective: The aim of the current study was to determine the impact of aging on hs-cTnT levels in elderly patients without acute cardiac events but in the presence of comorbidities.

Methods: Sociodemographic and clinical data were collected from 6977 medical records of patients aged ≥65 years without acute coronary events but for whom hs-cTnT measurements were available. The patients were stratified based on age, troponin levels and the number of comorbidities.

Results: The results suggested that the likelihood of increased hs-cTnT was related to the presence of comorbidities independently of their number ($p < 0.05$). The adjusted odds ratio (AOR) for both advanced age and having comorbidity was statistically significant, however for the old group (74 ≥ age ≥ 84 years) the chance of having elevated troponin regarding age compared to the presence of comorbidity was 1.070 *vs.* 1.216, whereas for the old-old group (≥85 years) it was found to be 1.071 *vs.* 1.311. Besides statistical significance for age, from a clinical standpoint, the AOR of 1.070 may not be considered clinically relevant.

Conclusion: Increased hs-cTnT levels were associated with the presence of pre-existing comorbidities independently of age. Increased hs-cTnT levels in the elderly should always be considered as pathological, and a specific etiology should be searched.

1. Introduction

Elderly patient, when experiencing myocardial infarction, frequently present with atypical symptoms, often lack chest pain, have non-diagnostic ECG and delay in diagnosis and treatment [1]. High sensitivity troponin can aid in the rightful diagnosis of primary type myocardial infarction (type 1/associated with primary coronary event) when interpreted appropriately. Making or excluding correctly a myocardial infarction diagnosis in due time is paramount, especially in the elderly population, since they are both prone to worse prognosis if left untreated and more complications from therapy than younger counterparts [2,3]. Correct interpretation of elevated troponin in the elderly requires understanding of the factors that influence the baseline level of that protein. Most of the available literature indicates a positive and independent association with aging and increased baseline troponin level, but few, if none, have compared directly the impact of aging itself to the comorbidity burden that may come with aging [4–6].

Coronary heart disease (CHD) events are well established as a leading cause of death among older people [7], but the relationships between age, comorbidities and the levels of cardiac biomarkers serving as indicators for cardiac events are still subject to debate. One such biomarker, cardiac troponin, is established as the best biomarker to detect myocardial necrosis [8].

With the growing clinical adoption of cardiac troponin, the diagnosis of acute myocardial infarction (AMI), or acute coronary syndrome (ACS), has shifted from a primarily clinical diagnosis predicated on electrocardiogram (ECG) findings and blood biomarker levels, to one essentially based on cardiac troponin assays, supported by clinical and ECG findings [9].

The importance of cardiac troponin becomes even more prominent in elderly patients [8], particularly those >80 years of age, for whom secondary diagnostic characteristics of ACS such as chest pain, electrocardiography, and biomarkers are often unreliable when trying to exclude AMI [10]. This is exacerbated by the high prevalence of multiple chronic

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conditions and comorbidities in elderly patients, which may result in "atypical" or "asymptomatic" presentations [11]. There is, however, only limited data about cTnT behavior in elderly patients, and even less knowledge about cTnT in the oldest bracket of patients with AMI in the presence of comorbidities [12]. Moreover, hs-cTnT assays have been shown to be associated with a higher frequency of false-positives for AMI in elderly patients [13]. As such, AMI misdiagnoses are frequent with very old patients [14] and an improved interpretation of elevated hs-cTnT in elderly patients with comorbidities could have a considerable influence on ACS risk stratification.

Our hypothesis is that, after excluding ACS in elderly patients, the increased cardiac troponin values are mainly associated with the presence of comorbidities and not with age. Therefore, the main objective of this research is to determine the differential effect of age and comorbidities on the increased plasma hs-cTnT levels in elderly patients without ACS.

2. Methodology

2.1. Patients selection and database records

This retrospective observational cohort study in geriatric Caucasian population was undertaken at the University Hospital of Sherbrooke (Quebec, Canada) (CHUS) using administrative database of patient records. Selected patients were aged ≥65 years, admitted to the university hospital between January 2012 and December 2016 and for whom serial analysis of hs-cTnT levels had been performed. Patient records were reviewed, and demographic, clinical and hs-cTnT data were extracted.

Data records were obtained for all patients admitted for emergency evaluation suspecting acute coronary events (chest pain, sweeting, palpitations, vomiting, dyspnoea). The exclusion of ACS was based on the same diagnostic criteria applied in our hospital, namely, the serial measurement of hsTnT (0, 2 h and 6 h) and also the ECG. The first statistical step of analysis contained 7080 medical records. The database was refined by detecting and or removing corrupt, inaccurate, or unnecessary records from our data pool. Our refined data then was reduced to a sample of 6822 medical records with the presence of multiple comorbidities in all. The study protocol was approved by the local Ethical Committee of the CIUSSS de l'Estrie-CHUS (approbation # 2018-2441).

2.2. Variables

The main dependent variables were hs-cTnT values and the occurrence of the following concomitant comorbidities: diabetes, heart failure (HF), chronic obstructive pulmonary disease (COPD), renal insufficiency, cancers, hypertension, neurocognitive disorders, hypothyroidism, anemia, cardiomyopathy, pulmonary hypertension, pulmonary embolism, pneumonia, stroke, atherosclerotic vascular disease, subarachnoid hemorrhage and other non-acute cardiovascular disease. Demographic and independent variables were age and sex.

2.3. Hs-cTnT assay

The hs-cTnT was measured using the elecrochemiluminescence immunoassays with Roche Elecsys analyzers (Troponin T Stat, Roche Diagnostics, F. Hoffmann-La Roche Ltd., Basel, Switzerland), with a limit of detection of 3 ng/L.

All patients for whom the diagnosis was MI or ACS have been automatically excluded. Therefore, for the included patients only the first hs-cTnT measurement, collected at time of admission to the hospital or emergency department, was considered.

2.4. Statistical analysis

Continuous variables were expressed as means ± standard deviation (SD), median and quartiles. Categorical variables were expressed as absolute values and percentages of the total. Independent *t*-test (to compare the troponin levels between age groups), Chi-square tests or Pearson $\chi 2$ tests (to evaluate the differences in the prevalence of comorbidities according to troponin levels) and multivariate logistic regression (to determine the association between the risk of having high troponin levels with age and comorbidities) were applied. Data were analyzed using SPSS (v24; IBM, USA). The statistical significance level was set at $P < 0.05$.

3. Results

A total of 6977 medical records of patients aged ≥65 years were included in the study database. After excluding all medical records with a history of cardiac arrest, previous or post-operative AMI and/or missing medical information, a final sample of 6822 elderly patients remained.

Table 1 presents the demographic and clinical characteristics of the study cohort. The cohort was categorized into three age groups: patients aged 65 to 74 years (young-old), aged 75 to 84 years (old) and aged ≥85 years (old-old). The average age of our sample was 78.3 years, with the oldest patient aged 104 years. Subjects were also divided into three categories according to the tertile of hs-cTnT concentration: tertile 1 (0–14 ng/L = low level: normal, according to the manufacturer instructions), tertile 2 (15–31 ng/L = moderate level) and tertile 3 (≥32 ng/L = high level). The mean hs-cTnT level in our total sample was 79.9 ng/L.

The cohort was further categorized according to the occurrence of comorbidities: quartile 1 (one or two comorbidities), quartile 2 (three comorbidities), quartile 3 (four or five comorbidities) and quartile 4 (≥6 comorbidities). A large number of subjects ($n = 2414$; 35.4%) had six or more comorbidities. Arterial hypertension and cardiomyopathy were the most and the least frequently observed comorbidities, respectively.

Table 2 presents total and by-sex mean hs-cTnT levels according to the comorbidity quartiles. The standard deviation of total and all quartile from the mean of troponin level was found relatively high due to the dispersion of troponin values. The mean hs-cTnT was considered high across sexes, age groups and comorbidity quartiles.

Table 1
Demographic and clinical characteristics of the study cohort.

Age: $\bar{x}$ ± SD	65–74 years old ($n = 2555$) 69 ± 2.83	75–84 years old ($n = 2490$) 79 ± 2.88	≥85 years old ($n = 1777$) 89 ± 3.62	All patients ($n = 6822$) 78.3 ± 8.30
Men (%)	1456 (57%)	1294 (52%)	649 (36%)	3439 (50.4%)
Women (%)	1098 (43%)	1196 (48%)	1128 (64%)	3383 (49.6%)
Hs-cTnT ng/L ($\bar{x}$ ± SD)	93 ± 312.15	77 ± 234.46	63 ± 162.73	79 ± 252.14
Men	104 ± 353.0	80 ± 183.73	70 ± 125.32	89 ± 264.64
Women	78 ± 242.34	74 ± 279.19	59 ± 180.71	70 ± 238.45
Comorbidities (N, %)				
Quartile I (1291, 19.4)				
Men	283.48	228.52	132.61	643.48
Women	349.52	207.48	83.49	684.52
Quartile II (1048, 15.4)				
Men	169.39	188.48	149.58	506.48
Women	263.61	204.52	78.42	545.52
Quartile III (2030, 19.8)				
Men	313.41	355.48	354.67	1022.51
Women	442.59	392.52	174.33	1008.49
Quartile IV (2414, 35.4)				
Men	294.43	425.46	493.61	1212.51
Women	397.56	491.54	314.39	1202.49

Hs-cTnT (High-sensitivity cardiac Troponin T), ng/L = nanogram/L Quartiles (I = 1–2 comorbidities, II = 3 comorbidities, III = 4–5 comorbidities, IV = ≥6 comorbidities).

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Table 2
Levels of hs-cTnT (ng/L) by sex and comorbidity quartiles.

	Total ($\bar{X} \pm SD$)	Men ($\bar{X} \pm SD$)	Women ($\bar{X} \pm SD$)	P-value
Q I	79 ± 324.68	93 ± 416.20	65 ± 181.78	p > 0.05
Q II	81 ± 290.86	89 ± 263.39	71 ± 317.80	p > 0.05
Q III	89 ± 264.02	97 ± 242.62	81 ± 283.43	p > 0.05
Q IV	71 ± 161.85	66 ± 203.50	76 ± 119.84	p > 0.05

Quartiles (I = 1–2 comorbidities, II = 3 comorbidities, III = 4–5 comorbidities, IV = ≥6 comorbidities), Hs-cTnT (High-sensitivity cardiac Troponin T), SD (standard deviation).

Table 3
Median and quartiles of hs-cTnT, by sex and age.

	Male	Female
	Median [Q1; Q3]	Median [Q1; Q3]
65–74 years	24.0 [13.0; 57.2]	19,0 [9.0; 45.2]
75–84 years	33.0 [19.0; 63.0]	24,0 [14.0; 48.0]
85+ years	39.0 [25.0; 67.2]	31,0 [20.0; 52.0]

Q1: 25 percentile; Q3: 75 percentiles.

According to our primary data analysis, the probability of having raised levels of troponin was increased with all types of comorbidities. In our pooled analysis of patients' medical records, plasma levels of hs-cTnT had a non-parametric distribution as the hs-cTnT values were abnormally distributed. In other words, the level of hs-cTnT was extremely dispersed above the reference range, that means a lot of patients had raised hs-cTnT level >33 ng/L whereas the standard deviation that was of greater magnitude than its mean. It can be exemplified by an individual with an Hs-cTnT value of 9258 ng/L (which would probably be clinically correct) which could influence the Mean ($\bar{x}$).

By analyzing hs-cTnT across age groups when corrected for comorbid disease there was a significant decrease of baseline hs-cTnT in male patients and an insignificant trend in female patients (Table 3).

When participants with elevated Hs-cTnT were compared with participants with troponin levels within the reference range using the adjusted odds ratio, there was a significantly increased probability of having an increased level of troponin in the moderate or high-level range that came with age but also with each comorbidity (Table 4). For example, male participants of >84 years old had a crude odds ratio of 5.61 ($p < 0.001$) for having an increased level of hs-cTnT but this did not account for comorbid diseases of that group (Table 4).

Table 5
Adjusted odds ratio for one comorbidity and for a year of aging.

Tertile of hs-cTnT	AOR	95% CI	P value
2			
Burden of disease	1.216	[1.178, 1.255]	p < 0.001
Age	1.070	[1.061, 1.080]	p < 0.001
3			
Burden of disease	1.311	[1.272, 1.352]	p < 0.001
Age	1.073	[1.064, 1.082]	p < 0.001

Reference category is: 1, CI = confidence interval. AOR = adjusted odds ratio.

In order to determine whether the observed increases in troponin were attributable to advancing age or the occurrence of comorbidities, adjusted OR (AOR) were included into our logistical regression model (Table 5). By analyzing the risk of having increased troponin levels with the adjusted odds ratio (AOR) still taking the population with normal troponin levels as the reference range, the relative impact of each added comorbidity surpasses the effect of one year of aging as shown in Table 4. Each year of aging confers an AOR of having a high level of hs-cTnT of 1.073 ($p < 0.001$) which is far less than the impact of one added comorbid disease which confers an AOR of 1.311 ($p < 0.001$).

The main disadvantage of the mean ($\bar{x}$) in statistical analysis refers to its susceptibility to the impact of outliners, so the mean cannot be representative of the values in the sample. Therefore, in this situation, it would be preferred to have a more accurate measure of central tendency. In this case, from a statistical point of view, the use of the Median [Q1: 25 percentile; Q3: 75 percentiles] which is not influenced by extreme values, seems more precise. Therefore, we applied the median to present Hs-cTnT values (interquartile range).

The occurrence of more comorbidity appears to have a greater influence on troponin levels, compared to age, in both hs-cTnT tertiles. In other words, among the elderly, age may not be a risk factor for increased cardiac troponin levels.

4. Discussion

Although the hs-cTnT is a marker that has made a significant contribution to the diagnosis of acute myocardial events, the interpretation of abnormal hs-cTnT levels remain as a debate among geriatric cardiologists. It could become a challenging clinical issue for the elderly patients with vague ischemic symptoms, atypical ECG and

Table 4
Odd ratios of having moderate or high levels of hs-cTnT in men and women, by age groups and the occurrence of comorbidities.

	Hs-cTnT (0-14 ng/L) = Low level			Hs-cTnT (15-31 ng/L) = moderate level			Hs-cTnT (≥32 ng/L) = high level		
Men	N = 666			N = 1125			N = 1648		
Women	N = 860			N = 1176			N = 1342		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Sum of the comorbidities for men	1.22	[1.16; 1.28]	p < 0.001	1.38	[1.31; 1.44]	p < 0.001			
Sum of the comorbidities for women	1.23	[1.18; 1.28]	p < 0.001	1.26	[1.21; 1.32]	p < 0.001			
Old group [75–84 years old]									
Men	2.03	[1.63; 2.52]	p < 0.001	2.13	[1.73; 2.63]	p < 0.001			
Women	1.53	[1.25; 1.89]	p < 0.001	1.70	[1.37; 2.10]	p < 0.001			
Old-old group [≥85 years old]									
Men	4.49	[3.10; 6.50]	p < 0.001	5.61	[3.92; 8.03]	p < 0.001			
Women	4.45	[3.42; 5.70]	p < 0.001	4.55	[3.53; 5.82]	p < 0.001			
Young-old group [65–74 years old]									
Men	1			1					
Women	1			1					

Reference group: 1, CI = confidence interval. Multivariate logistic regressions were performed to quantify the risk of having a high level of troponin according to age and comorbidities. For both the old and old-old age groups and for both sexes, we observed a greater risk of having higher levels of hs-cTnT. After calculating odds ratio, with each increase in age, in all age groups of both sexes, the risk of having a moderate and high level of hs-cTnT has shown to be increased.

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abnormal cTnT levels, to diagnose whether the patient suffer from ACS, since it is proven that certain adverse outcomes due to acute coronary events increase with age [15].

This study aimed to determine the influence of age on the value of hs-cTnT in older adults without acute cardiac events, but with one or more comorbidities, to improve the diagnostic prediction of acute coronary events in elderly.

The results of the present study have shown that, in elderly and very elderly patients suffering from different comorbidities, the presence of comorbidities compared with advancing age has more effect to rising hs-cTnT level. In other words, the raised cardiac troponin in the absence of AMI or ACS in the elderly population resulted from the presence of comorbidities and not from their age.

The main significant novelty of the present study is to exclude acute cardiac events (ACE) in order to eliminate the role of cardiac injury on increasing hs-cTnT levels, and to consider the comorbidities in the sample pools as well. That means that the effects of advancing age and ACE, as confounding biases, are diminished.

In our literature review, among the comorbidities that have been included in the different studies, almost all papers indicated that the renal dysfunction and congestive heart failure are the main reasons for the increased hs-cTnT values in geriatric patients [16,17].

In almost all previous similar studies where the individuals were screened to rule out ACS, the majority of these studies have justified the increased hs-cTnT level as related to the advanced age if the ACS could be excluded. Although in these studies the comorbidities were presented, the authors only indicated that the reason for the increased hs-cTnT levels was the advanced age [8,18–25]. In other words, the age has been considered as the main factor for explaining the elevated hs-cTnT.

Although a few studies have suggested the influence of comorbidities on raised hs-cTnT, they were still more attributed to the effect of advancing age [26]. Several studies have considered the influence of age on hs-cTnT as significant; consequently, they have underestimated the diagnostic role of hs-cTnT assay in ACE profiles [16,17]. While, our data analysis suggests a different interpretation of the rising hs-cTnT levels in elderly, namely the hs-cTnT could still be a sensitive and very useful acute cardiac biomarker to detect acute coronary events, and could play a more significant role in ACS diagnosis in aged patients, mainly in old-old patients if other reasons of its elevation are taken into consideration such as other causes (co-morbidities) leading to increased hs-cTnT levels.

A study of factors affecting hs-cTnT values has shown that the hs-cTnT levels are higher in men and increases with age in both men and women [27]. Our results fit with the first part of mentioned study, which means that the basic levels of hs-cTnT are increased in men compared to women, but in contrast our results have shown that the hs-cTnT levels are not showing clinically significant change with advancing age in both sexes.

As the previous studies have significantly interpreted the elevated of hs-cTnT values as an effect of advancing age [13,19], our data analysis shows that the possible causes of the increased hs-cTnT in elderly population are the presence of different comorbidities, and not advancing age. Our results are also not in agreement with those of Kuster et al. showing that hs-cTnT concentration, independently of comorbidities, increases exponentially with age after 65 years [6]. However, in their study the authors had used Cox regression to analyze their data which was not possible in our condition due to abnormal distribution of the hs-cTnT values. If the elevated hs-cTnT value considered as a result of advancing age, it may be assumed that the hs-cTnT assay is not a reliable criterion to exclude ACE in diagnosis of geriatric patients. However, at the absence of a thrombotic complication of coronary artery disease in elderly patients, an elevated hs-cTnT could be the result of undiagnosed comorbidities. Considering our pool of patients, it could be concluded that among elderly patients of either sex, with abnormal hs-cTnT values, older patients were more likely to have an elevated troponin level compared to the younger cohorts due to the presence of comorbidities, but not to age ($p < 0.001$).

To our knowledge, this is the first study to document that advancing age has a less role to play in elderly patients with high hs-cTnT concentrations. Based on the results of the present study, the elevated levels of hs-cTnT in aged patients without any ACE are further due to other causes which should be thoroughly investigated.

5. Conclusion

It is shown that there is an overall increase of hs-cTnT values in all groups of elderly patients with comorbidities. Our findings suggest that in elderly patients the association of elevated hs-cTnT is mostly explained by the presence of comorbidity than by advancing age. Consequently, an increased hs-cTnT value in an elderly subject that is not associated to the occurrence of ACS should be always be investigated for other underlying clinical problems.

6. Study strengths

In the current study, our sample size was large, so in our statistical analysis the *t*-test has so much power that even a minuscule difference was flagged as statistically significant. On the other hand, we recruited the medical records of a large heterogeneous elderly population, who were divided into three main aged groups with seventeen comorbidities, so our results could be applied or generated to represent group of elderly patients, as a whole. Thus, the main result of the study showing that age is not the main cause for hs-cTnT can be most probably generalized.

7. Study limitations

In our study, the evaluation of hs-cTnT accuracy was limited since the data was collected only on elderly patients with different comorbidities, without having much awareness of their concomitant therapy. In other words, it is not possible to quantify the presence of different comorbidity, how much it could increase the level of hs-cTnT values. Therefore, we cannot speculate the variance of the hs-cTnT values in elderly patients who were affected by different concomitant diseases with respect to their comorbidity.

Lastly, in this study, although the data were included from a large cohort of patients, these data are observational.

8. Future directions

Features of acute coronary events in elderly and very elderly patients comprise life-threatening conditions that require immediate and efficient medical intervention to improve prospective outcomes, particularly in the presence of atypical signs and symptoms. Judicious interpretation of increased hs-cTnT levels is essential in different fields of medicine, particularly in emergency wards, intensive care units and geriatric cardiology. Clinical assessment with use of para-clinical data is critical for an accurate and prompt diagnosis followed by appropriate management. Thoughtful interpretation of hs-cTnT levels may yield insight into physio-pathological mechanism of the concomitant condition that causes the raised hs-cTnT in elderly. Furthermore, future directions should aim to find the cut-off level for hs-cTnT levels at the presence of different comorbidities in acute coronary events, and study the relationship between mortality and increased levels of troponin in elderly patients with different comorbidities as well.

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Conflict of interest

- The authors do not declare any competing interest.
- A part of these results was presented as a poster at the ESC Congress 2018, Munich, Germany.

Disclosures

No actual or potential conflict of interest in relation to this study to declare. We also testify that we have no relationships with industry in connection with this study.

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